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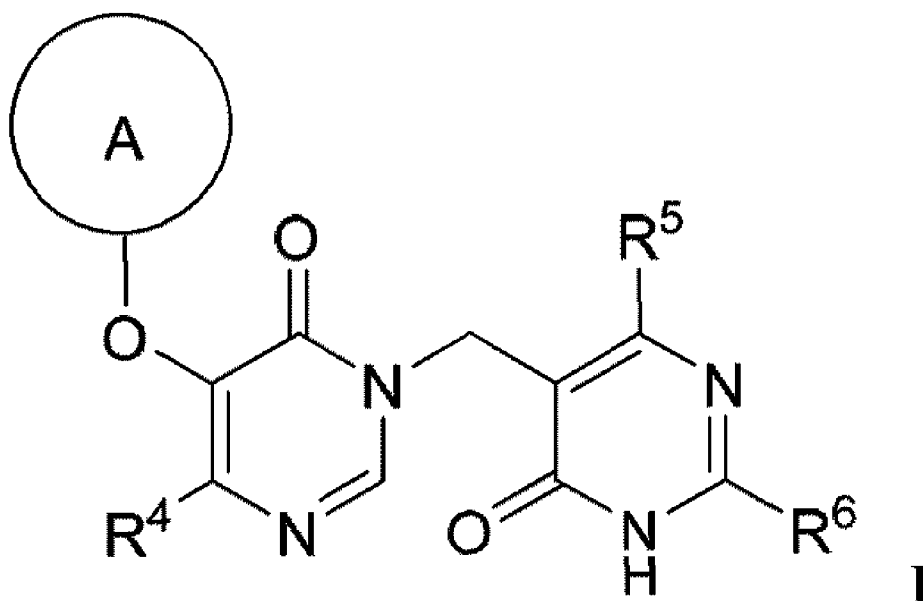
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(54) **Titre : DERIVES DE PYRIMIDONE EN TANT QU'AGENTS CYTOTOXIQUES SELECTIFS CONTRE DES CELLULES INFECTEES PAR LE VIH**

(54) **Title: PYRIMIDONE DERIVATIVES AS SELECTIVE CYTOTOXIC AGENTS AGAINST HIV INFECTED CELLS**



(57) **Abrégé/Abstract:**

The present disclosure is directed to pyrimidone derivatives of Formula I and their use for selectively killing HIV infected GAG-POL expressing cells without concomitant cytotoxicity to HIV nave cells, and for the treatment or prophylaxis of infection by HIV, or for the treatment, prophylaxis or delay in the onset or progression of AIDS or AIDS Related Complex (ARC).



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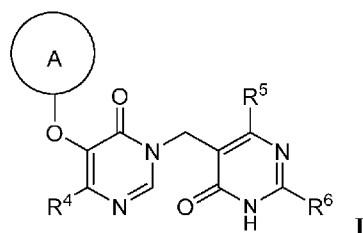
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(54) Title: PYRIMIDONE DERIVATIVES AS SELECTIVE CYTOTOXIC AGENTS AGAINST HIV INFECTED CELLS



(57) Abstract: The present disclosure is directed to pyrimidone derivatives of Formula I and their use for selectively killing HIV infected GAG-POL expressing cells without concomitant cytotoxicity to HIV nave cells, and for the treatment or prophylaxis of infection by HIV, or for the treatment, prophylaxis or delay in the onset or progression of AIDS or AIDS Related Complex (ARC).



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TITLE OF THE INVENTION

PYRIMIDONE DERIVATIVES AS SELECTIVE CYTOTOXIC AGENTS AGAINST HIV
INFECTED CELLS

5 BACKGROUND OF THE INVENTION

Human immunodeficiency virus (HIV) is the causative agent of acquired immunodeficiency syndrome (AIDS). In the absence of viral suppression, humans infected with HIV exhibit severe immunodeficiency which makes them highly susceptible to debilitating and ultimately fatal opportunistic infections. Multiple clinically approved antiretroviral drugs are available which demonstrate multi-log reductions in viral loads. Treated patients are at risk for acquiring mutations which render the virus in their bodies resistant to available therapies and rapid rebound of viremia is seen when therapy is removed, indicating that current regimens are not curative.

HIV is a retrovirus whose life cycle involves reverse transcription of a viral RNA genome into DNA via an enzyme known as reverse transcriptase and subsequent integration of the DNA copy into the host chromosomal DNA via the virally encoded integrase. Viral RNA is transcribed and viral proteins are translated using the host cellular machinery in conjunction with viral accessory proteins. Many viral proteins are contained within the GAG and GAG-POL proteins, with GAG containing structural proteins and GAG-POL resulting from a frameshift near the carboxy-terminus of GAG and containing protease (PR), reverse transcriptase (RT), and integrase (IN) viral enzymes, in addition to the structural proteins. GAG and GAG-POL are cleaved into individual proteins through the process of maturation which occurs during budding of virions from the infected cell. At this time GAG-POL dimerizes and the now dimeric HIV PR within the GAG-POL dimer forms an active enzyme which can cleave itself out of the polypeptide and catalyze further cleavage to form the remaining viral enzymes and structural proteins.

Available antiretroviral drugs act by blocking the virus at different stages in the viral life cycle. For example, reverse transcriptase inhibitors target the viral reverse transcriptase and prevent the RNA genome from being copied into DNA, integrase inhibitors block the ability of the copied DNA from being integrated into the host cell, and protease inhibitors prevent viral

maturation so that virions produced from cells treated with protease inhibitors are immature and non-infectious. Once integration has occurred, a cell is infected until it dies through either normal cell death pathways, accelerated death due to viral factors, or is targeted by the immune system. While most infected cells are expected to die within ~2 days of being infected, the rapid
5 rebound of viremia when therapy is removed is an indication that infected cells remain even after years on therapy (*See, e.g., J. B. Dinoso et al., Proc. Natl. Acad. Sci. U.S.A., 2009, 106(23): 9403-9408*). Thus, new therapies that can selectively kill the HIV infected cells would provide new treatment options for HIV infection. Treatment with compounds that can accelerate death of HIV infected cells and decrease the overall number of virally infected cells that persist within
10 patients have the potential to decrease low-level viremia in suppressed patients and may also play a role in an HIV cure strategy.

SUMMARY OF THE INVENTION

The present disclosure is directed to pyrimidone derivatives and their use as HIV-
15 Targeted Activator of Cell Kill agents which accelerate the death of HIV GAG-POL expressing cells without concomitant cytotoxicity to HIV naïve cells. Accordingly, the compounds disclosed herein are useful for the treatment or prophylaxis of infection by HIV, or for the treatment, prophylaxis or delay in the onset or progression of AIDS or AIDS Related Complex (ARC). Additionally, the compounds are useful for selectively killing HIV infected GAG-POL
20 expressing cells in a subject infected with HIV. Compositions and methods of use comprising the compounds of this disclosure are also provided.

DETAILED DESCRIPTION OF THE INVENTION

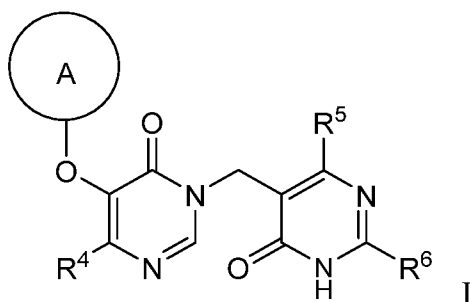
The present disclosure is directed to pyrimidone derivative compounds and their
25 use for accelerating the death of HIV GAG-POL expressing cells without concomitant cytotoxicity to HIV naïve cells. In the absence of compounds such as those from the present invention, protease (PR) activation takes place during viral maturation and the concentration of mature PR in the cytoplasm is limited. In contrast, the present compounds promote the desired phenotype by catalyzing GAG-POL dimerization inside the infected cell by binding to the
30 immature RT binding site and triggering premature activation of the HIV PR enzyme inside the

host infected cell prior to budding. As a result, PR cleaves host substrates within the cell, leading to cytotoxicity and cell death. This effect can be blocked in the presence of an HIV protease inhibitor such as indinavir or darunavir demonstrating the role of HIV protease in the process.

5 The compounds presently disclosed herein also have activity as Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs), due to the homology between the mature and immature RT pocket in HIV that allows the compounds to bind to the mature hydrophobic pocket near the active site of the viral RT enzyme. Binding to mature RT results in inhibition of enzymatic activity and production of the DNA provirus, which prevents infection of naïve CD4+
10 T-cells.

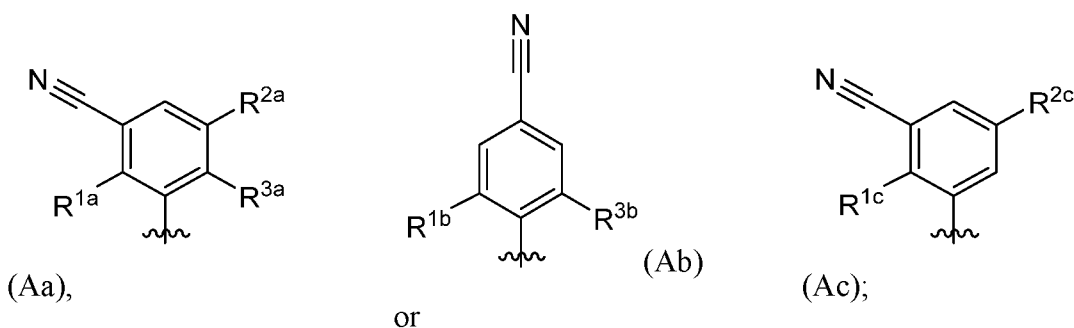
 While effects of NNRTIs on dimerization of RT and GAG-POL have been documented (Tachedjian et al. Proc. Natl. Acad. Sci. U.S.A. 2001, 98(13):7188; Tachedjian et al. FEBS Lett. 2005, 579:379; Figueiredo et al. PLOS Path. 2006, 2(11):1051; Sudo et al. J. Virol. 2013, 87(6):3348), selective killing of HIV infected cells as a result of enhanced dimerization
15 was first reported by Jochmans et al. (Jochmans et al. Retrovirology 2010, 7:89). The authors generated data showing these effects in chronically infected MT-4 cells, PBMCs, and CD4+ cells. Based on the potencies of tested molecules they concluded that “These data present proof of concept for targeted drug induced elimination of HIV producing cells. While NNRTIs themselves may not be sufficiently potent for therapeutic application, the results provide a basis
20 for the development of drugs exploiting this mechanism of action.” More recently, Zerbato *et al.* (Zerbato *et al.* Antimicrob. Agents Chemother. 2017, 61(3)) measured the activity of NNRTIs in a primary cell model for HIV latency. They saw significant reduction in virus production for certain NNRTIs compared to other classes of antiretrovirals and inferred that this was due to these compounds’ ability to eliminate cells expressing HIV GAG-POL proteins. More recently,
25 Trinité *et al.* (Trinité *et al.*, Retrovirology, 2019, 16(17)) documented how NNRTI-induced PR-activation triggers apoptotic cell death of productively HIV-infected resting or activated T-cells.

 The present disclosure is directed to a compound of Formula I



or a pharmaceutically acceptable salt thereof, wherein:

Ring A is selected from:



R^{1a} is halo, -C₁₋₃alkyl unsubstituted or substituted with 1 to 7 of F; -OC₁₋₃alkyl unsubstituted
 5 or substituted with 1 to 7 of F; or -NH₂, -NH-C₁₋₃alkyl, -N(C₁₋₃alkyl)₂, or -C₃₋₆cycloalkyl;

R^{2a} is -H, halo, -C₁₋₃alkyl, -CF₃, -CHF₂, -CH₂F, -NH₂, -NH-C₁₋₃alkyl, -N(C₁₋₃alkyl)₂, -C₃₋₆cycloalkyl or -OC₁₋₃alkyl unsubstituted or substituted with 1 to 3 of F;

R^{3a} is -H or halo;

provided that R^{2a} and R^{3a} are not both -H;

10

R^{1b} is halo, -C₁₋₃alkyl, -CF₃, -CHF₂, -CH₂F, -NH₂, -NH-C₁₋₃alkyl, -N(C₁₋₃alkyl)₂,
 -C₃₋₆cycloalkyl, or -OC₁₋₃alkyl unsubstituted or substituted with 1 to 3 of F;

R^{3b} is halo, -C₁₋₃alkyl, -CF₃, -CHF₂, -CH₂F, -NH₂, -NH-C₁₋₃alkyl, -N(C₁₋₃alkyl)₂,
 -C₃₋₆cycloalkyl, or -OC₁₋₃alkyl unsubstituted or substituted with 1 to 3 of F;

15

R^{1c} is -H, halo, -C₁₋₃alkyl, -CF₃, -CHF₂, -CH₂F, -NH₂, -NH-C₁₋₃alkyl, -N(C₁₋₃alkyl)₂,
 -C₃₋₆cycloalkyl, or -OC₁₋₃alkyl unsubstituted or substituted with 1 to 3 of F;

R^{2c} is -H, halo, -C₁₋₃alkyl, -CF₃, -CHF₂, -CH₂F, -NH₂, -NH-C₁₋₃alkyl, -N(C₁₋₃alkyl)₂, -C₃₋₆cycloalkyl, or -OC₁₋₃alkyl unsubstituted or substituted with 1 to 3 of F; provided that one of R^{1c} or R^{2c} is -H and the other is not -H;

- 5 R⁴ is halo or -C₁₋₆alkyl substituted with 1 to 8 of -F;
 R⁵ is -H, -NH₂, -NH-C₁₋₃alkyl, -N(C₁₋₃alkyl)₂, -C₃₋₆cycloalkyl, or -C₁₋₃alkyl unsubstituted or substituted with 1 to 7 of -F;
 R⁶ is -H, -C₁₋₄alkyl, -C₂₋₄alkenyl, -NH₂, -NH-C₁₋₃alkyl, -N(C₁₋₃alkyl)₂, C₃₋₆cycloalkyl, -pyrazolyl unsubstituted or substituted with C₁₋₃alkyl, or -C₁₋₄alkyl substituted with R⁷; and
 10 R⁷ is -OH, -OC₁₋₃alkyl, -C(O)OC₁₋₃alkyl or -CH₂O-pyrimidinyl.

In Embodiment 1 of this disclosure are compounds of Formula I, or pharmaceutically acceptable salts thereof, wherein:

- (i) R⁴ is -C₁₋₆alkyl substituted with 1 to 8 of -F; or
 15 (ii) R⁴ is -CF₃, or -C₂₋₆alkyl substituted with 1 to 8 of -F; or
 (iii) R⁴ is -C₂₋₆alkyl substituted with 1 to 8 of -F; or
 (iv) R⁴ is -C₂₋₄alkyl substituted with 1 to 8 of -F; or
 (v) R⁴ is -CH(F)-R⁸ or -C(F₂)-R⁸ wherein R⁸ is (a) -CH₃ unsubstituted or substituted with 1 to 3 of -F, or (b) -CH₂CH₃ unsubstituted or substituted with 1 to 5 of -F; or
 20 (vi) R⁴ is -CH(F)CH₃, -CH(F)CH₂F, -CH(F)CHF₂, -CH(F)CF₃, -CF₂CH₃, -CF₂CH₂F, -CF₂CHF₂ or -CF₂CF₃.

In Embodiment 2 of this disclosure are compounds of Formula I or Embodiment 1, or pharmaceutically acceptable salts thereof, wherein:

- (i) R⁵ is -H, -NH₂, -C₃₋₄cycloalkyl, or -C₁₋₃alkyl unsubstituted or substituted with 1 to 7 of -F;
 25 or
 (ii) R⁵ is -H, -NH₂, -cyclopropyl, -CH₃ unsubstituted or substituted with 1 to 3 of -F, or -CH₂CH₃ substituted with 1 to 5 of -F; or

(iii) R⁵ is -H or -CH₃ unsubstituted or substituted with 1 to 3 of -F.

In Embodiment 3 of this disclosure are compounds of Formula I, Embodiment 1 or Embodiment 2, or pharmaceutically acceptable salts thereof, wherein:

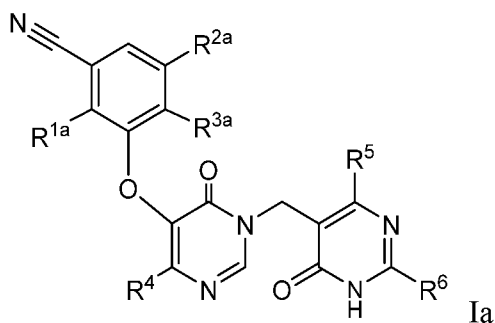
(i) R⁶ is -H, -C₁₋₄alkyl, -CH=C(C₁₋₃alkyl)₂, -NH₂, -NH-C₁₋₃alkyl, -N(C₁₋₃alkyl)₂, or

5 -C₁₋₄alkyl substituted with R⁷; and R⁷ is -OH, -OC₁₋₃alkyl or -C(O)OC₁₋₃alkyl; or

(ii) -H, -C₁₋₃alkyl (e.g., CH₃), -C₁₋₄alkyl-OR⁷, -C₁₋₃alkyl-COOH, -C₂₋₄alkenyl, -NH₂ and pyrazolyl unsubstituted or substituted with C₁₋₃alkyl, wherein R⁷ is -H, -C₁₋₃alkyl-OCH₃ or -CH₂O-pyrimidinyl; or

(iii) -CH₃, -C₁₋₄alkyl-OH, or -C(O)OCH₃.

10 In Embodiment 4 of this disclosure are compounds of Formula I, Embodiment 1, Embodiment 2, or Embodiment 3, wherein Ring A is (Aa) having the following Formula Ia:



or a pharmaceutically acceptable salt thereof.

15 In Embodiment 4A of this disclosure are compounds of Formula I, Formula Ia, Embodiment 1, Embodiment 2, Embodiment 3, or Embodiment 4, or pharmaceutically acceptable salts thereof, wherein:

(i) R^{1a} is -F, -Cl, Br, -C₁₋₃alkyl, -CF₃, -CHF₂, -CH₂F, -NH₂, -C₃₋₄cycloalkyl or -OC₁₋₃alkyl unsubstituted or substituted with 1 to 3 of F; and R^{2a} is -H, -F, -Cl, Br, -C₁₋₃alkyl, -CF₃, -CHF₂, -CH₂F, -NH₂, -C₃₋₄cycloalkyl or -OC₁₋₃alkyl unsubstituted or substituted with 1 to 3

20 of F; provided that R^{2a} and R^{3a} are not both -H; or

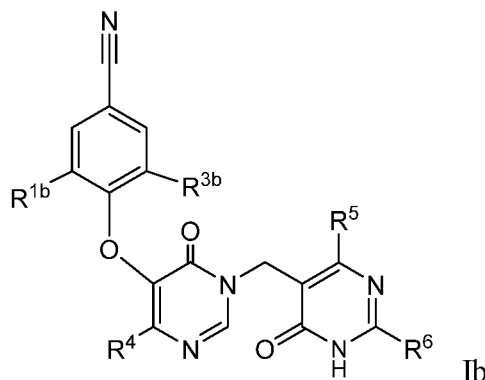
(ii) R^{3a} is -H, -F, -Cl or Br, provided that R^{2a} and R^{3a} are not both -H; or

(iii) R^{1a} and R^{2a} are each independently -F, -Cl, Br, -C₁₋₃alkyl, -CF₃, -CHF₂, CH₂F, or -OC₁₋₃alkyl unsubstituted or substituted with 1 to 3 of F; and R^{3a} is -H, -F, -Cl or Br, or R^{3a} is H.

In Embodiment 4B of this disclosure are compounds of Formula I, Formula Ia, Embodiment 1, Embodiment 2, Embodiment 3, Embodiment 4, or Embodiment 4A, or pharmaceutically acceptable salts thereof, wherein:

R⁴ is -CH(F)-R⁸ or -C(F₂)-R⁸ wherein R⁸ is (a) -CH₃ unsubstituted or substituted with 1 to 3 of F, or (b) -CH₂CH₃ unsubstituted or substituted with 1 to 5 of -F.

In Embodiment 5 of this disclosure are compounds of Formula I, Embodiment 1, Embodiment 2, or Embodiment 3, wherein Ring A is (Ab) having the following Formula Ib:



or a pharmaceutically acceptable salt thereof.

In Embodiment 5A of this disclosure are compounds of Formula I, Formula Ib, Embodiment 1, Embodiment 2, Embodiment 3, or Embodiment 5, or pharmaceutically acceptable salts thereof, wherein:

(i) R^{1b} is halo, -C₁₋₃alkyl, -CF₃, -CHF₂, -CH₂F, -C₃₋₄cycloalkyl, or -OC₁₋₃alkyl unsubstituted or substituted with 1 to 3 of F; or

(ii) R^{3b} is halo, -C₁₋₃alkyl, -CF₃, -CHF₂, -CH₂F, -C₃₋₄cycloalkyl, or -OC₁₋₃alkyl unsubstituted or substituted with 1 to 3 of F; or

(iii) R^{1b} and R^{3b} are each independently halo, -C₁₋₃alkyl, -CF₃, -CHF₂, -CH₂F, -C₃₋₄cycloalkyl, or -OC₁₋₃alkyl unsubstituted or substituted with 1 to 3 of F;

(iv) R^{1b} and R^{3b} are each independently -F, -Cl, -CH₃, -CF₃, -CHF₂, -CH₂F, -C₃₋₄cycloalkyl, or -OC₁₋₃alkyl unsubstituted or substituted with 1 to 3 of F.

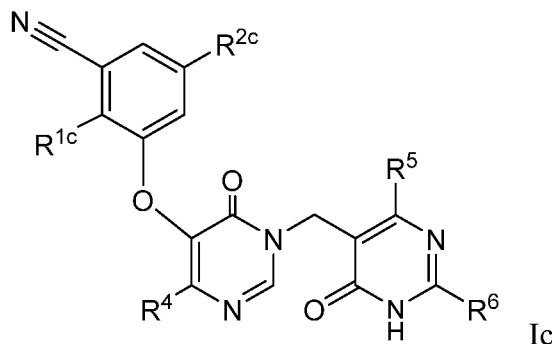
In Embodiment 5B of this disclosure are compounds of Formula I, Formula Ib, Embodiment 1, Embodiment 2, Embodiment 3, or Embodiment 5, or pharmaceutically acceptable salts thereof, wherein:

- (i) R^{1b} is -F, -Cl, -CH₃, -CF₃, -CHF₂, -CH₂F, -OCH₃ or cyclopropyl; or
- (ii) R^{3b} is -F, -Cl, -CH₃, -CF₃, -CHF₂, -CH₂F, -OCH₃ or cyclopropyl; or
- (iii) R^{1b} and R^{3b} are each independently -F, -Cl, -CH₃, -CF₃, -CHF₂, -CH₂F, -OCH₃ or cyclopropyl.

In Embodiment 5C of this disclosure are compounds of Formula I, Formula Ib, Embodiment 1, Embodiment 2, Embodiment 3, Embodiment 5, or Embodiment 5A, or Embodiment 5B, or pharmaceutically acceptable salts thereof, wherein:

R⁴ is -CF₃, -CH(F)-R⁸ or -C(F₂)-R⁸ wherein R⁸ is (a) -CH₃ unsubstituted or substituted with 1 to 3 of F, or (b) -CH₂CH₃ unsubstituted or substituted with 1 to 5 of -F.

In Embodiment 6 of this disclosure are compounds of Formula I, Embodiment 1, Embodiment 2, or Embodiment 3, wherein Ring A is (Ac) having the following Formula Ic:



or a pharmaceutically acceptable salt thereof.

In Embodiment 6A of this disclosure are compounds of Formula I, Formula Ic, Embodiment 1, Embodiment 2, Embodiment 3 or Embodiment 6, or pharmaceutically acceptable salts thereof, wherein:

- (i) R^{1c} is -H, halo, -CH₃, -CF₃, -CHF₂ or -CH₂F; or

(ii) R^{2c} is -H, halo, -CH₃, -CF₃, -CHF₂ or -CH₂F; or

(iii) R^{1c} and R^{2c} are each independently -H, halo, -CH₃, -CF₃, -CHF₂ or -CH₂F;

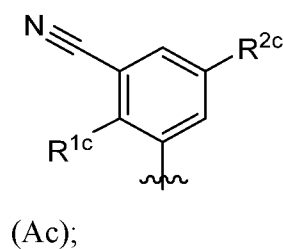
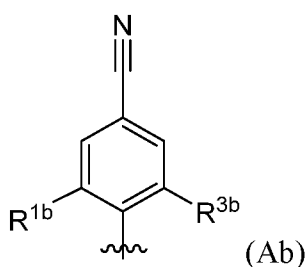
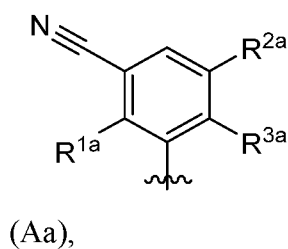
provided that one of R^{1c} or R^{2c} is -H and the other is not -H.

5 In Embodiment 6B of this disclosure are compounds of Formula I, Formula Ic, Embodiment 1, Embodiment 2, Embodiment 3, Embodiment 6, or Embodiment 6A, or pharmaceutically acceptable salts thereof, wherein:

R^4 is -CH(F)- R^8 or -C(F₂)- R^8 wherein R^8 is (a) -CH₃ unsubstituted or substituted with 1 to 3 of -F, or (b) -CH₂CH₃ unsubstituted or substituted with 1 to 5 of -F.

10 In Embodiment 7 are compounds of Formula I or a pharmaceutically acceptable salt thereof, wherein:

Ring A is selected from:



or

R^{1a} is halo (e.g., F, Cl, Br), -C₁₋₃alkyl (e.g. -CH₃), -OC₁₋₃alkyl unsubstituted or substituted with 1-3 of F (e.g. -OCH₃), or -NH₂;

15 R^{2a} is -H, halo (e.g., F, Cl, Br), -C₁₋₃alkyl unsubstituted or substituted with 1-6 of F (e.g., -CH₃, -CH₂CH₃, -CF₃, -CH₂F, -CHF₂);

R^{3a} is -H or halo (e.g., F, Cl, Br);

provided that R^{2a} and R^{3a} are not both -H;

R^{1b} is halo (e.g., F, Cl, Br), -C₁₋₃alkyl (e.g. -CH₃), -OC₁₋₃alkyl (e.g. -OCH₃), -CF₃, or

20 -C₃₋₆cycloalkyl (e.g., cyclopropyl);

R^{3b} is halo or -C₁₋₃alkyl unsubstituted or substituted with 1-6 of F (e.g., -CH₃, -CH₂CH₃, -CF₃, -CH₂F, -CHF₂);

R^{1c} is -H, halo (e.g., F, Cl, Br) or -C₁₋₃alkyl (e.g., -CH₃, -CH₂CH₃);

R^{2c} is -H, halo (e.g., F, Cl, Br), -C₁₋₃alkyl unsubstituted or substituted with 1 to 6 of -F (e.g., -CH₃, -CH₂CH₃, -CF₃, -CH₂F, -CHF₂);

provided that one of R^{1c} or R^{2c} is -H and the other is not -H;

5 R⁴ is halo (e.g., F, Cl, Br), or -C₁₋₃alkyl substituted with 1 to 6 of -F (e.g., -CF₃, -CH₂F, -CHF₂, -CF₂CH₃, -CF₂CHF₂, -CF₂CF₃, -CH₂CH₃ substituted with 1-5 of F)

R⁵ is -H, -NH₂, -C₃₋₆cycloalkyl (e.g., cyclopropyl), or -C₁₋₃alkyl unsubstituted or substituted with 1 to 6 of -F;

10 R⁶ is -H, -C₁₋₃alkyl (e.g., CH₃), -C₁₋₄alkyl-OR⁷, -C₁₋₃alkyl-COOH, -C₂₋₄alkenyl, -NH₂ and pyrazolyl unsubstituted or substituted with C₁₋₃alkyl, wherein R⁷ is -H, -C₁₋₃alkyl-OCH₃ or -CH₂O-pyrimidinyl.

15 Reference to the compounds of Formula I herein encompasses the compounds of Formula I, Ia, Ib and Ic, and all embodiments, classes and sub-classes thereof and includes the compounds of the Examples herein. The compounds of Formula I encompass neutral compounds or salts thereof when such salts are possible, including pharmaceutically acceptable salts.

20 The term “e.g.” means “for example.” When the terms “e.g.” or “for example” are used herein, the example(s) recited are intended to be illustrative and are not intended to be an exhaustive list of all relevant examples.

25 As used herein, “alkyl” refers to both branched- and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms in a specified range. For example the term “C₁₋₆alkyl” means linear or branched chain alkyl groups, including all possible isomers, having 1, 2, 3, 4, 5 or 6 carbon atoms, and includes each of the hexyl and pentyl isomers as well as *n*-, *iso*-, *sec*- and *tert*-butyl (butyl, *i*-butyl, *s*-butyl, *t*-butyl, collectively “C₄alkyl”; Bu = butyl), *n*- and *i*-propyl (propyl, *i*-propyl, collectively “C₃alkyl”; Pr = propyl), ethyl (Et) and methyl (Me). “C₁₋₄alkyl” has 1, 2, 3 or 4 carbon atoms and includes each of *n*-, *i*-,

s- and *t*-butyl, *n*- and *i*-propyl, ethyl and methyl. "C₁₋₃alkyl" has 1, 2 or 3 carbon atoms and includes each of *n*-propyl, *i*-propyl, ethyl and methyl.

"Cycloalkyl" refers to a cyclized alkyl ring having the indicated number of carbon atoms in a specified range. Thus, for example, "C₃₋₆cycloalkyl" includes each of cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl, and "C₃₋₄cycloalkyl" includes each of cyclopropyl and cyclobutyl.

"Halo" or "halogen" refers to chloro, fluoro, bromo or iodo. Chloro, fluoro and bromo are a class of halogens of interest, and more particularly fluoro.

"HIV naïve cell(s)" are cells that are not infected with HIV.

"Compatible anti-HIV agent(s)" are anti-HIV agents excluding HIV protease inhibitors.

A "stable" compound is a compound which can be prepared and isolated and whose structure and properties remain or can be caused to remain essentially unchanged for a period of time sufficient to allow use of the compound for the purposes described herein (e.g., therapeutic or prophylactic administration to a subject). The compounds of the present disclosure are limited to stable compounds embraced by Formula I and its embodiments. For example, certain moieties as defined in Formula I may be unsubstituted or substituted, and the latter is intended to encompass substitution patterns (i.e., number and kind of substituents) that are chemically possible for the moiety and that result in a stable compound.

This disclosure includes individual diastereomers, particularly epimers, i.e., compounds having the same chemical formula but which differ in the spatial arrangement around a single atom. This disclosure also includes mixtures of diastereomers, particularly mixtures of epimers, in all ratios. This disclosure encompasses compounds of Formula I having either the (*R*) or (*S*) stereo-configuration at an asymmetric center and at any additional asymmetric centers that may be present in a compound of Formula I, as well as stereo-isomeric mixtures thereof. Embodiments of this disclosure also include a mixture of enantiomers enriched with 51% or more of one of the enantiomers, including for example 60% or more, 70% or more, 80% or more, or 90% or more of one enantiomer. A single epimer is preferred. An individual or single enantiomer refers to an enantiomer obtained by chiral synthesis and/or using generally known separation and purification techniques, and which may be 100% of one enantiomer or may

contain small amounts (e.g., 10% or less) of the opposite enantiomer. Thus, individual enantiomers are a subject of this disclosure in pure form, both as levorotatory and as dextrorotatory antipodes, in the form of racemates and in the form of mixtures of the two enantiomers in all ratios. In the case of a cis/trans isomerism this disclosure includes both the cis
5 form and the trans form as well as mixtures of these forms in all ratios.

The preparation of individual stereoisomers can be carried out, if desired, by separation of a mixture by customary methods, for example by chromatography or crystallization, by the use of stereochemically uniform starting materials for the synthesis or by stereoselective synthesis. Optionally a derivatization can be carried out before a separation of stereoisomers.

10 The separation of a mixture of stereoisomers can be carried out at an intermediate step during the synthesis of a compound of Formula I or it can be done on a final racemic product. Absolute stereochemistry may be determined by X-ray crystallography of crystalline products or crystalline intermediates which are derivatized, if necessary, with a reagent containing a stereogenic center of known configuration. Alternatively, absolute stereochemistry may be
15 determined by Vibrational Circular Dichroism (VCD) spectroscopy analysis. The present disclosure includes all such isomers, as well as salts, solvates (which includes hydrates). and solvated salts of such racemates, enantiomers, diastereomers and tautomers and mixtures thereof.

As would be recognized by one of ordinary skill in the art, certain compounds of the present disclosure may be able to exist as tautomers. All tautomeric forms of such
20 compounds, whether isolated individually or in mixtures, are within the scope of the present disclosure. For example, in instances where an oxo (=O) substituent is permitted on a heteroaromatic ring and keto-enol tautomerism is possible, it is understood that the substituent might in fact be present, in whole or in part, in the -OH form.

The atoms in a compound of Formula I may exhibit their natural isotopic
25 abundances, or one or more of the atoms may be artificially enriched in a particular isotope having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number predominantly found in nature. The present disclosure is meant to include all suitable isotopic variations of the compounds of Formula I; for example, different isotopic forms of hydrogen (H) include protium (^1H) and deuterium (^2H). Protium is the predominant
30 hydrogen isotope found in nature. Enriching for deuterium may afford certain therapeutic

advantages, such as increasing *in vivo* half-life or reducing dosage requirements, or may provide a compound useful as a standard for characterization of biological samples. Isotopically-enriched compounds of Formula I can be prepared without undue experimentation by conventional techniques well known to those skilled in the art or by processes analogous to those described in the Schemes and Examples herein using appropriate isotopically-enriched reagents and/or intermediates.

The compounds can be administered in the form of pharmaceutically acceptable salts. The term "pharmaceutically acceptable salt" refers to a salt which possesses the effectiveness of the parent compound and which is not biologically or otherwise undesirable (e.g., is neither toxic nor otherwise deleterious to the recipient thereof). When the compounds of Formula I contain one or more acidic groups or basic groups, the invention includes the corresponding pharmaceutically acceptable salts.

Thus, the compounds of Formula I that contain acidic groups (e.g., -COOH) can be used according to the invention as, for example but not limited to, alkali metal salts, alkaline earth metal salts or as ammonium salts. Examples of such salts include but are not limited to sodium salts, potassium salts, calcium salts, magnesium salts or salts with ammonia or organic amines such as, for example, ethylamine, ethanolamine, triethanolamine or amino acids. Compounds of Formula I, which contain one or more basic groups, i.e. groups which can be protonated, can be used according to the invention in the form of their acid addition salts with inorganic or organic acids as, for example but not limited to, salts with hydrogen chloride, hydrogen bromide, phosphoric acid, sulfuric acid, nitric acid, benzenesulfonic acid, methanesulfonic acid, p-toluenesulfonic acid, naphthalenedisulfonic acids, oxalic acid, acetic acid, trifluoroacetic acid, tartaric acid, lactic acid, salicylic acid, benzoic acid, formic acid, propionic acid, pivalic acid, diethylacetic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, malic acid, sulfaminic acid, phenylpropionic acid, gluconic acid, ascorbic acid, isonicotinic acid, citric acid, adipic acid, etc. If the compounds of Formula I simultaneously contain acidic and basic groups in the molecule the invention also includes, in addition to the salt forms mentioned, inner salts or betaines (zwitterions). Salts can be obtained from the compounds of Formula I by customary methods which are known to the person skilled in the art, for example by combination with an organic or inorganic acid or base in a solvent or dispersant, or by anion

exchange or cation exchange from other salts. The present invention also includes all salts of the compounds of Formula I which, owing to low physiological compatibility, are not directly suitable for use in pharmaceuticals but which can be used, for example, as intermediates for chemical reactions or for the preparation of pharmaceutically acceptable salts.

5 The instant disclosure encompasses any composition comprised of a compound of Formula I or a compound that is a salt thereof, including for example but not limited to, a composition comprised of said compound associated together with one or more additional molecular and/or ionic component(s) which may be referred to as a "co-crystal." The term "co-crystal" as used herein refers to a solid phase (which may or may not be crystalline) wherein two
10 or more different molecular and/or ionic components (generally in a stoichiometric ratio) are held together by non-ionic interactions including but not limited to hydrogen-bonding, dipole-dipole interactions, dipole-quadrupole interactions or dispersion forces (van der Waals). There is no proton transfer between the dissimilar components and the solid phase is neither a simple salt nor a solvate. A discussion of co-crystals can be found, e.g., in S. Aitipamula et al., *Crystal*
15 *Growth and Design*, 2012, 12 (5), pp. 2147–2152.

Furthermore, compounds of the present disclosure may exist in amorphous form and/or one or more crystalline forms, and as such all amorphous and crystalline forms and mixtures thereof of the compounds of Formula I and salts thereof are intended to be included within the scope of the present disclosure. In addition, some of the compounds of the instant
20 disclosure may form solvates with water (i.e., a hydrate) or common organic solvents. Such solvates and hydrates, particularly the pharmaceutically acceptable solvates and hydrates, of the compounds of this disclosure are likewise encompassed within the scope of the compounds defined by Formula I and the pharmaceutically acceptable salts thereof, along with un-solvated and anhydrous forms of such compounds.

25 Accordingly, the compounds of Formula I or salts thereof including pharmaceutically acceptable salts thereof, embodiments thereof and specific compounds described and claimed herein, encompass all possible stereoisomers, tautomers, physical forms (e.g., amorphous and crystalline forms), co-crystal forms, solvate and hydrate forms, and any combination of the foregoing forms where such forms are possible.

Another embodiment of the present disclosure is a compound of Formula I wherein the compound or its salt is in a substantially pure form. As used herein "substantially pure" means suitably at least about 60 wt.%, typically at least about 70 wt.%, preferably at least about 80 wt.%, more preferably at least about 90 wt.% (e.g., from about 90 wt.% to about 99 wt.%), even more preferably at least about 95 wt.% (e.g., from about 95 wt.% to about 99 wt.%, or from about 98 wt. % to 100 wt. %), and most preferably at least about 99 wt.% (e.g., 100 wt.%) of a product containing a compound of Formula I or its salt (e.g., the product isolated from a reaction mixture affording the compound or salt) consists of the compound or salt. The level of purity of the compounds and salts can be determined using a standard method of analysis such as, high performance liquid chromatography, and/or mass spectrometry or NMR techniques. If more than one method of analysis is employed and the methods provide experimentally significant differences in the level of purity determined, then the method providing the highest purity level governs. A compound or salt of 100% purity is one which is free of detectable impurities as determined by a standard method of analysis. With respect to a compound of the invention which has one or more asymmetric centers and can occur as mixtures of stereoisomers, a substantially pure compound can be either a substantially pure mixture of the stereoisomers or a substantially pure individual stereoisomer.

The compounds of Formula I herein, and pharmaceutically acceptable salts thereof, are useful for eliciting GAG-POL dimerization in HIV-infected cells and thereby selectively killing HIV infected GAG-POL expressing cells without concomitant cytotoxicity to HIV naïve cells, referred to herein as TACK (Targeted Activator of Cell Kill) activity, or more specifically HIV TACK activity . HIV TACK or TACK have also been previously referred to as Small Molecule Activated Cell Kill (SMACK). Thus, the compounds of Formula I and pharmaceutically acceptable salts thereof are useful for:

- (i) A method for the treatment or prophylaxis of infection by HIV, or for the treatment, prophylaxis, or delay in the onset or progression of AIDS or ARC in a human subject in need thereof which comprises administering to the human subject an effective amount of the compound according to Formula I, or a pharmaceutically acceptable salt thereof;

(ii) A method for eliciting GAG-POL dimerization in HIV-infected cells in a human subject in need thereof which comprises administering to the human subject an effective amount of the compound according to Formula I, or a pharmaceutically acceptable salt thereof; and/or

(iii) A method for selectively killing HIV infected GAG-POL expressing cells without
5 concomitant cytotoxicity to HIV naïve cells in a human subject which comprises administering to the human subject an effective amount of the compound according to Formula I, or a pharmaceutically acceptable salt thereof.

Additionally, the compounds of Formula I and pharmaceutically acceptable salts thereof are useful for any of the methods (i), (ii) or (iii) above, further comprising administering
10 to the human subject an effective amount of one or more compatible HIV antiviral agents selected from nucleoside or nucleotide HIV reverse transcriptase inhibitors, nucleoside reverse transcriptase translocation inhibitors, non-nucleoside HIV reverse transcriptase inhibitors, HIV integrase inhibitors, HIV fusion inhibitors, HIV entry inhibitors, HIV maturation inhibitors and post-attachment inhibitors. In the methods of (i), (ii) or (iii) immediately above, the human
15 subject can be treated with a compound Formula I or a pharmaceutically acceptable salt thereof in addition to treatment with one or more compatible HIV antiviral agents.

The compounds of Formula I and pharmaceutically acceptable salts thereof are also useful for a method for augmenting the suppression of HIV viremia in a human subject whose viremia is being suppressed by administration of one or more compatible HIV antiviral
20 agents, which comprises additionally administering to the human subject an effective amount of the compound according to Formula I, or a pharmaceutically acceptable salt thereof.

Other embodiments of the present disclosure include the following:

(a) A pharmaceutical composition comprising an effective amount of a compound of Formula I or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable
25 carrier.

(b) A pharmaceutical composition which comprises the product prepared by combining (e.g., mixing) an effective amount of a compound of Formula I or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

(c) The pharmaceutical composition of (a) or (b), further comprising an effective amount of one or more compatible anti-HIV agents selected from the group consisting of HIV antiviral agents, immunomodulators, and anti-infective agents.

(d) The pharmaceutical composition of (c), wherein the compatible anti-HIV agent is selected from one or more of an antiviral selected from the group consisting of nucleoside or nucleotide HIV reverse transcriptase inhibitors, nucleoside HIV reverse transcriptase translocation inhibitors, non-nucleoside HIV reverse transcriptase inhibitors, HIV integrase inhibitors, HIV fusion inhibitors, HIV entry inhibitors, HIV maturation inhibitors and post attachment inhibitors.

(e) A combination which is (i) a compound of Formula I or a pharmaceutically acceptable salt thereof and (ii) one or more compatible anti-HIV agents selected from the group consisting of HIV antiviral agents, immunomodulators, and anti-infective agents; wherein the compound and the compatible anti-HIV agent are each employed in an amount that renders the combination effective for the treatment or prophylaxis of infection by HIV, or for the treatment, prophylaxis or delay in the onset or progression of AIDS or ARC.

(f) The combination of (e), wherein the compatible anti-HIV agent is an antiviral selected from the group consisting of nucleoside or nucleotide HIV reverse transcriptase inhibitors, nucleoside reverse transcriptase translocation inhibitors, non-nucleoside HIV reverse transcriptase inhibitors, HIV integrase inhibitors, HIV fusion inhibitors, HIV entry inhibitors, HIV maturation inhibitors and post attachment inhibitors.

(g) A method for eliciting GAG-POL dimerization in HIV-infected cells, a method for selectively killing HIV infected GAG-POL expressing cells without concomitant cytotoxicity to HIV naïve cells, and/or a method for the treatment or prophylaxis of infection by HIV, or for the treatment, prophylaxis, or delay in the onset or progression of AIDS or ARC, comprising administering an effective amount of a compound of Formula I or a pharmaceutically acceptable salt thereof to a subject in need of such treatment.

(h) The method of (g), wherein the compound of Formula I or a pharmaceutically acceptable salt thereof is administered in combination with an effective amount of at least one other compatible HIV antiviral selected from nucleoside or nucleotide HIV reverse transcriptase inhibitors, nucleoside reverse transcriptase translocation inhibitors, non-nucleoside HIV reverse

transcriptase inhibitors, HIV integrase inhibitors, HIV fusion inhibitors, HIV entry inhibitors, HIV maturation inhibitors and post attachment inhibitors.

(i) The method of (g) or (h) comprising administering to the subject the pharmaceutical composition of (a), (b), (c) or (d) or the combination of (e) or (f).

5 (j) Use of a compound of Formula I or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for (1) eliciting GAG-POL dimerization in HIV-infected cells in a subject; (2) selectively killing HIV infected GAG-POL expressing cells without concomitant cytotoxicity to HIV naïve cells in a subject; (3) treatment or prophylaxis of infection by HIV in a subject; (4) treatment, prophylaxis or delay in the onset or progression of AIDS or ARC in a
10 subject; (5) augmenting the suppression of HIV viremia in a subject undergoing treatment with a compatible anti-HIV agent, and/or (6) augmenting the suppression of HIV viremia in a subject whose viremia is being suppressed by administration of one or more compatible HIV antiviral agents.

(k) A compound of Formula I, or a pharmaceutically acceptable salt thereof, for use
15 in (1) eliciting GAG-POL dimerization in HIV-infected cells; (2) selectively killing HIV infected GAG-POL expressing cells without concomitant cytotoxicity to HIV naïve cells; (3) treatment or prophylaxis of infection by HIV; (4) the treatment, prophylaxis or delay in the onset or progression of AIDS or ARC; and/or (5) augmenting the suppression of HIV viremia in a subject undergoing treatment with a compatible anti-HIV agent.

20 Additional embodiments of the present invention include each of the pharmaceutical compositions, methods and uses set forth in the preceding paragraphs, wherein the compound of Formula I or its salt employed therein is substantially pure. With respect to a pharmaceutical composition comprising a compound of Formula I or its salt and a pharmaceutically acceptable carrier and optionally one or more excipients, it is understood that
25 the term "substantially pure" is in reference to a compound of Formula I or its salt per se.

In another embodiment of the present disclosure are the pharmaceutical compositions, methods and uses set forth above, wherein the HIV of interest is HIV-1.

An additional embodiment of the present invention includes the pharmaceutical compositions, methods, medicaments, uses and combinations set forth herein, wherein the HIV
30 of interest is HIV-1. Thus, for example, in any of the pharmaceutical compositions, methods,

medicaments, uses and combinations using the compounds of Formula I or pharmaceutically acceptable salts thereof, the compound or salt thereof is employed in an amount effective against HIV-1; and when used in combination with one or more compatible anti-HIV agent(s), each such additional agent is a compatible HIV-1 antiviral selected from one or more of nucleoside or
5 nucleotide HIV reverse transcriptase inhibitors, nucleoside reverse transcriptase translocation inhibitors, non-nucleoside HIV reverse transcriptase inhibitors, HIV integrase inhibitors, HIV fusion inhibitors, HIV entry inhibitors, HIV maturation inhibitors and post-attachment inhibitors.

The term "administration" and variants thereof (e.g., "administering" a compound) in reference to a compound of Formula I means providing the compound to the
10 individual in need of treatment or prophylaxis and includes both self-administration and administration to the patient by another person or any other means. When a compound is provided in combination with one or more other active agents (e.g., antiviral agents useful for treating or prophylaxis of HIV infection or AIDS), "administration" and its variants are each understood to include provision of the compound and other agents at the same time or at
15 different times. When the agents of a combination are administered at the same time, they can be administered together in a single composition or they can be administered separately.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients, as well as any product which results from combining the specified ingredients. Ingredients suitable for inclusion in a pharmaceutical composition are
20 pharmaceutically acceptable ingredients, which means the ingredients must be compatible with each other and not deleterious to the recipient thereof.

The term "subject" or "patient" as used herein refers to a human (or "person") who has been the object of treatment, observation or experiment. Examples of patients to be treated with an HIV TACK agent include but are not limited to, patients who have been infected
25 with HIV, and/or HIV infected patients whose HIV viral load has been suppressed and/or is considered to be undetectable at time of HIV TACK treatment. Patients to be treated with an HIV TACK agent also include, but are not limited to, those using an HIV TACK agent for prophylaxis of HIV infection or for post-exposure prophylaxis after being potentially exposed to HIV to prevent becoming infected.

“Prophylaxis” includes each of pre-exposure prophylaxis (PrEP), i.e., using a compound of Formula I or a pharmaceutically acceptable salt thereof to prevent HIV infection in a person who does not have HIV, and post-exposure prophylaxis (PEP), i.e., using a compound of Formula I or a pharmaceutically acceptable salt thereof after being potentially exposed to HIV
5 to prevent becoming infected with HIV.

The term "effective amount" as used herein means an amount of a compound sufficient to elicit GAG-POL dimerization in HIV-infected cells and selectively kill HIV infected GAG-POL expressing cells without concomitant cytotoxicity to HIV naïve cells; and/or exert a therapeutic effect, and/or a exert a prophylactic effect after administration. One embodiment of
10 “effective amount” is a "therapeutically effective amount" which is an amount of a compound that is effective for selectively killing HIV infected GAG-POL expressing cells, effective for treating HIV infection, or effective for the treatment, prophylaxis or delay in the onset or progression of AIDS or ARC in a patient infected with HIV. Another embodiment of “effective amount” is a "prophylactically effective amount" which is an amount of the compound that is
15 effective for prophylaxis of HIV infection, or prophylaxis of AIDS or ARC in an HIV-infected patient. It is understood that an effective amount can simultaneously be both a therapeutically effective amount, e.g., for treatment of HIV infection, and a prophylactically effective amount, e.g., for prevention or reduction of risk for developing AIDS or ARC in a subject infected with HIV.

20 In the combination therapies of the present invention, an effective amount can refer to each individual agent or to the combination as a whole, wherein the amounts of all agents administered in the combination are together effective, but wherein a component agent of the combination may or may not be present individually in an effective amount with reference to what is considered effective for that component agent if it were administered alone.

25 In the methods of the present invention., (i.e., selectively killing HIV infected GAG-POL expressing cells, the treatment of infection by HIV, prophylaxis of HIV infection or the treatment, prophylaxis or delay in the onset or progression of AIDS or ARC), the compounds of this invention, or salts thereof, can be administered by means that produce contact of the active agent with the agent's site of action. They can be administered by conventional means
30 available for use in conjunction with pharmaceuticals, either as individual therapeutic agents or

in a combination of therapeutic agents. The compound can be administered itself, but typically is administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice. The compounds of the invention can, for example, be administered orally (e.g., via tablet or capsule), parenterally (including subcutaneous injections, intravenous, intramuscular or intrasternal injection, or infusion techniques), by inhalation spray, or rectally, in the form of a unit dosage of a pharmaceutical composition containing an effective amount of the compound and conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The compound could also be administered via an implantable drug delivery device adapted to provide an effective amount of the compound or a pharmaceutical composition of the compound over an extended period of time.

FORMULATIONS

Solid preparations suitable for oral administration (e.g., powders, pills, capsules and tablets) can be prepared according to techniques known in the art and can employ such solid excipients as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like. Liquid preparations suitable for oral administration (e.g., suspensions, syrups, elixirs and the like) can be prepared according to techniques known in the art and can employ any of the usual media such as water, glycols, oils, alcohols and the like. Parenteral compositions can be prepared according to techniques known in the art and typically employ sterile water as a carrier and optionally other ingredients, such as a solubility aid. Injectable solutions can be prepared according to methods known in the art wherein the carrier comprises a saline solution, a glucose solution or a solution containing a mixture of saline and glucose. Implantable compositions can be prepared according to methods known in the art wherein the carrier comprises the active chemical ingredient with polymers and suitable excipients, or utilizing an implantable device for drug delivery. Further description of methods suitable for use in preparing pharmaceutical compositions for use in the present invention and of ingredients suitable for use in said compositions is provided in Remington - The Science and Practice of Pharmacy, 22nd Edition, published by Pharmaceutical Press and Philadelphia College of Pharmacy at University of the Sciences, 2012, ISBN 978 0 85711-062-6 and prior editions.

Formulations of compounds of Formula I that result in drug supersaturation and/or rapid dissolution may be utilized to facilitate oral drug absorption. Formulation

approaches to cause drug supersaturation and/or rapid dissolution include, but are not limited to, nanoparticulate systems, amorphous systems, solid solutions, solid dispersions, and lipid systems. Such formulation approaches and techniques for preparing them are known in the art. For example, solid dispersions can be prepared using excipients and processes as described in reviews (e.g., A.T.M. Serajuddin, J Pharm Sci, 88:10, pp. 1058-1066 (1999)). Nanoparticulate systems based on both attrition and direct synthesis have also been described in reviews such as Wu et al (F. Kesisoglou, S. Panmai, Y. Wu, Advanced Drug Delivery Reviews, 59:7 pp. 631-644 (2007)).

The compounds of Formula I may be administered in a dosage range of, e.g., 1 to 20 mg/kg, or 1 to 10 mg/kg, or about 5 mg/kg of mammal (e.g., human) body weight per day, or at other time intervals as appropriate, in a single dose or in divided doses. The compounds of Formula I may be administered in a dosage range of 0.001 to 2000 mg. per day in a single dose or in divided doses. Examples of dosage ranges are 0.01 to 1500 mg per day, or 0.1 to 1000 mg per day, administered orally or via other routes of administration in a single dose or in divided doses.

For oral (e.g., tablets or capsules) or other routes of administration, the dosage units may contain 100 mg to 1500 mg of the active ingredient, for example but not limited to, 100, 150, 200, 250, 300, 350, 400, 450, 500, 600, 700, 800, 900, 1000, 1100, 1200, 1300, 1400 or 1500 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. Furthermore, the compound may be formulated in oral formulations for immediate or modified release such as extended or controlled release. When the compound of Formula I is administered as a salt, reference to an amount of the compound in milligrams or grams is based on the free form (i.e., the non-salt form) of the compound.

Daily administration can be via any suitable route of administration but is preferably via oral administration and can be a single dose or more than one dose at staggered times (divided daily doses) within each 24-hour period. Each dose may be administered using one or multiple dosage units as appropriate.

The specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight,

general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy. In some cases, depending on the potency of the compound or the individual response, it may be necessary to deviate upwards or downwards from the given dose. The amount and frequency of
 5 administration will be regulated according to the judgment of the attending clinician considering such factors.

An "anti-HIV agent" is any agent which is directly or indirectly effective in the inhibition of HIV, the treatment or prophylaxis of HIV infection, and/or the treatment, prophylaxis or delay in the onset or progression of AIDS or ARC. It is understood that an anti-
 10 HIV agent is effective in treating, preventing, or delaying the onset or progression of HIV infection or AIDS and/or diseases or conditions arising therefrom or associated therewith. The present disclosure is additionally directed to use of a compound of Formula I or pharmaceutically acceptable salts thereof, with one or more compatible anti-HIV agents, i.e., anti-HIV agents excluding HIV protease inhibitors. For example, the compounds of Formula I may be
 15 administered in combination with effective amounts of one or more compatible anti-HIV agents selected from HIV antiviral agents, immunomodulators, anti-infectives, or vaccines useful for treating HIV infection or AIDS. Suitable compatible HIV antivirals for use in combination with the compounds of the present disclosure include, but are not limited to, those listed in Table A as follows:

TABLE A: Antiviral Agents for Treating HIV infection or AIDS

Name	Type
abacavir, ABC, ZIAGEN®	NRTI
abacavir + lamivudine, EPZICOM®	NRTI
abacavir + lamivudine + zidovudine, TRIZIVIR®	NRTI
AZT, zidovudine, azidothymidine, RETROVIR®	NRTI
bictegravir	InSTI
bictegravir + tenofovir alafenamide fumarate + emtricitabine, BIKTARVY®	InSTI/NRTI/NRTI

capravirine	NNRTI
ddC, zalcitabine, dideoxycytidine, HIVID®	NRTI
ddI, didanosine, dideoxyinosine, Videx®	NRTI
ddI (enteric coated), VIDEX EC®	NRTI
delavirdine, DLV, RESCRIPTOR®	NNRTI
dolutegravir, TIVICAY®	InSTI
dolutegravir + abacavir + lamivudine, TRIUMEQ®	InSTI/NRTI /NRTI
doravirine, PIFELTRO™	NNRTI
doravirine/lamivudine/tenofovir disoproxil fumarate, DELSTRIGO™	NNRTI/NRTI/NRTI
efavirenz, EFV, SUSTIVA®, STOCRIN®	NNRTI
Efavirenz/emtricitabine/tenofovir disoproxil fumarate, ATRIPLA®	NNRTI/ NRTI/NRTI
EFdA (4'-ethynyl-2-fluoro-2'-deoxyadenosine)	NRTTI
Elvitegravir, VITEKTA®	InSTI
emtricitabine, FTC, EMTRIVA®	NRTI
emtricitabine + tenofovir disoproxil fumarate, TRUVADA®	NRTI/NRTI
emivirine, COACTINON®	NNRTI
enfuvirtide, FUZEON®	FI
enteric coated didanosine, VIDEX EC®	NRTI
etravirine, TMC-125	NNRTI
Ibalizumab-uiyk (TROGARZO®)	Post-Attachment Inhibitor or Monoclonal Antibody
lamivudine, 3TC, EPIVIR®	NRTI
lamivudine + zidovudine, COMBIVIR®	NRTI/NRTI
maraviroc, SELZENTRY®	EI

nevirapine, NVP, VIRAMUNE®	NNRTI
raltegravir, ISENTRESS™	InSTI
rilpivirine, EDURANT®	NNRTI
stavudine, d4T, didehydrodeoxythymidine, ZERIT®	NRTI
tenofovir disoproxil fumarate (TDF), VIREAD®	NRTI
tenofovir alafenamide fumarate (TAF)	NRTI
victiviroc	EI

EI = entry inhibitor; FI = fusion inhibitor; InSTI = integrase inhibitor; NRTI = nucleoside or nucleotide reverse transcriptase inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTTI = nucleoside reverse transcriptase translocation inhibitor. Some of the drugs listed in the table are used in a salt form; e.g., abacavir sulfate, delavirdine mesylate.

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It is understood that the scope of combinations of the compounds of this invention with compatible anti-HIV agents is not limited to the HIV antivirals listed in Table A, but includes in principle any combination with any pharmaceutical composition useful for the treatment or prophylaxis of HIV AIDS, or ARC, with the exception of HIV protease inhibitors. The compatible HIV antiviral agents and other active agents will typically be employed in these combinations in their conventional dosage ranges and regimens as reported in the art, including, for example, the dosages described in the current Physicians' Desk Reference, Thomson PDR, 70th edition (2016), Montvale, NJ: PDR Network, or in prior editions thereof. The dosage ranges for a compound of the disclosure in these combinations can be the same as those set forth above.

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The compounds of this invention are also useful in the preparation and execution of screening assays for antiviral compounds. For example, the compounds of this invention are useful for isolating enzyme mutants, which are excellent screening tools for more powerful antiviral compounds. Furthermore, the compounds of this invention are useful in establishing or determining the binding site of other antivirals to the reverse transcriptase region within GAG-POL, e.g., by competitive inhibition.

The following acronyms and abbreviations have the indicated meanings:

ACN = acetonitrile
AcOH = acetic acid
aq. = aqueous
B ₂ Pin ₂ = bis(pinacolato)diboron
BPO = benzoyl peroxide
CAN = ceric ammonium nitrate
cataCXium A Pd G2 precatalyst = chloro[(di(1-adamantyl)- <i>N</i> -butylphosphine)-2-(2-aminobiphenyl)]palladium(II);
DAST = (diethylamino)sulfur trifluoride
DCE = 1,2-dichloroethane
DCM = dichloromethane
DDQ = 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIAD = diisopropyl azodicarboxylate
DHP = 3,4-dihydro-2 <i>H</i> -pyran
DIBAL-H = diisobutylaluminum hydride
DIPEA - diisopropylethylamine
DME = dimethoxyethane
DMF = <i>N,N</i> -dimethylformamide
Dess-Martin periodinane = 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1 <i>H</i>)-one
DMSO = dimethyl sulfoxide
DMSO- <i>d</i> ₆ = deuterated dimethyl sulfoxide
e.g. = for example, but not limited to
EDC = 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
EDTA = ethylenediaminetetraacetic acid
EtOAc = ethyl acetate

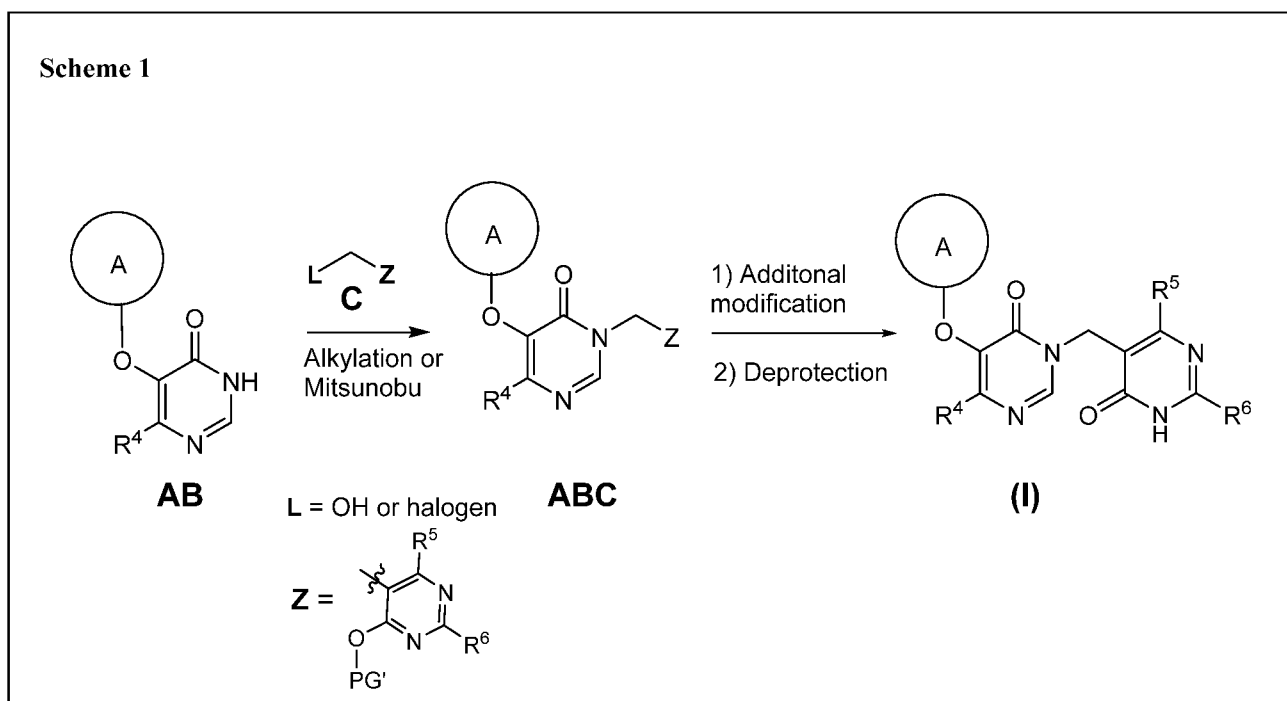
EtOH = ethanol
FBS = fetal bovine serum
GFP = Green fluorescent protein
HIV = human immunodeficiency virus
HOBt = hydroxybenzotriazole
HPLC = high performance liquid chromatography
h = hour
Int = intermediate
Ir [(Ome)(1,5-COD)] ₂ = (1,5-Cyclooctadiene)(methoxy)iridium(I) dimer
LCAP = liquid chromatography area percent
LC-MS = liquid chromatography-mass spectroscopy
LDA = lithium diisopropylamide
LAH = lithium aluminium hydride
m-CPBA = 3-chloroperbenzoic acid
Me = methyl
MeI = methyl iodide
MeOH = methanol
Me-THF = 2-methyltetrahydrofuran
MTBE = methyl tertiary-butyl ether
min = minute
MS = mass spectroscopy
MsCl = methanesulfonyl chloride
NBS = <i>N</i> -bromosuccinimide
n-BuLi = n-butyl lithium
NCS = <i>N</i> -chlorosuccinimide

NHS = normal human serum
NMP = <i>N</i> -methyl-2-pyrrolidinone
NMR = nuclear magnetic resonance
PBMC = peripheral blood mononuclear cell
PBS = phosphate buffered saline
$\text{Pd}_2(\text{dba})_3$ = tris(dibenzylideneacetone)dipalladium(0)
$\text{PdCl}_2(\text{dppf})$ = [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)
$\text{Pd}(\text{OAc})_2$ = palladium(II) acetate
$\text{Pd}(\text{Ph}_3\text{P})_4$ = tetrakis(triphenylphosphine)palladium(0)
P.E. = petroleum ether
PHA = phytoheagglutinin
PMB = 4-methoxybenzyl
PMBCl = 4-methoxybenzyl chloride
PPTS = 4-toluenesulfonic acid
RT = room temperature
$\text{S}_\text{N}\text{Ar}$ = nucleophilic aromatic substitution
TBAF = tetrabutylammonium fluoride
Tc = thiophene carboxylate
<i>t</i> -BuOH = <i>tert</i> -butanol
<i>t</i> -BuOK = potassium <i>tert</i> -butoxide
<i>t</i> -buXPhos Pd G3 precatalyst = [(2-di- <i>tert</i> -butylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)-2-(2'-amino-1,1'-biphenyl)] palladium(II) methanesulfonate
TEA = triethylamine
TFA = trifluoroacetic acid
TFAA = trifluoroacetic anhydride

THF = tetrahydrofuran
TLC = thin layer chromatography
TMS-Cl = trimethylsilyl chloride
X-Phos = 2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl

Several methods for preparing the compounds of this invention are described in the following Schemes and Examples. Starting materials and intermediates are purchased or are made using known procedures, or as otherwise illustrated in the five Intermediate (A, B, C, AB and BC) sections that follow. A frequently applied route to the compounds of Formula I are described in the Schemes that follow.

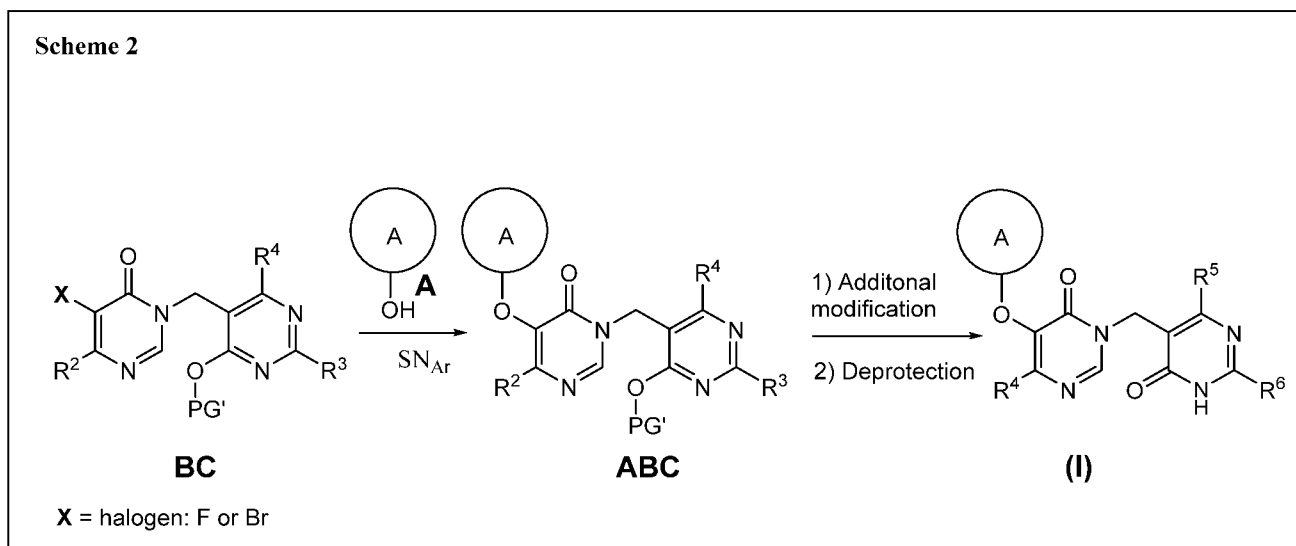
SCHEME 1



10 Scheme 1 depicts a method for preparing compounds of Formula I. Intermediate AB is prepared with procedures illustrated in the Intermediate AB section. Mitsunobu reaction or alkylation using an appropriate pyrimidinone benzylic alcohol or halide (Intermediate C) provides Intermediate ABC. Intermediate C usually has a protected pyrimidinone moiety shown as Z in Scheme 1. Synthesis of C is illustrated in the Intermediate C section. The resulting Intermediate

ABC may optionally undergo additional modification, followed by a deprotection step to afford compounds of Formula I.

SCHEME 2



Scheme 2 illustrates another method for preparing compounds of Formula I. An SN_{Ar} reaction between a phenol A (either commercially available or prepared using procedures in the Intermediate A section) and an Intermediate BC (made by procedures illustrated in the Intermediate BC section) is used to make Intermediate ABC. The pyrimidone C ring is generally protected with a protecting group (PG') such as methyl or a PMB group. The resulting Intermediate ABC may then optionally undergo additional modification followed by a deprotection step to afford compounds of Formula I.

Reactions sensitive to moisture or air were performed under nitrogen or argon using anhydrous solvents and reagents. Reactions performed using microwave irradiation were normally carried out using an Emrys Optimizer manufactured by Personal Chemistry, or an Initiator manufactured by Biotage. Concentration of solutions was carried out on a rotary evaporator under reduced pressure.

The progress of reactions was determined by either analytical thin layer chromatography (TLC) usually performed with E. Merck pre-coated TLC plates, silica gel 60F-254, layer thickness 0.25 mm or analytical liquid chromatography-mass spectrometry (LC-MS). Typically, the analytical LC-MS system used consisted of a Waters ZQ™ platform with electrospray

ionization in positive ion detection mode with an Agilent 1100 series HPLC with autosampler. The column was commonly a Waters Xterra MS C18, 3.0 × 50 mm, 5 μm or a Waters Acquity UPLC® BEH C18 1.0 x 50 mm, 1.7 μm. The flow rate was 1 mL/min, and the injection volume was 10 μL. UV detection was in the range 210–400 nm. The mobile phase consisted of solvent A (water plus 0.05% TFA) and solvent B (acetonitrile plus 0.05% TFA) with a gradient of 100% solvent A for 0.7 min changing to 100% solvent B over 3.75 min, maintained for 1.1 min, then reverting to 100% solvent A over 0.2 min. LC/MS determinations were carried out on a Waters Classing Aquity system equipped with TUV and MS detectors and a Waters SQD mass spectrometer, a Shimadzu 20 UV 254 and 220nm with Shimadzu 2010 or 2020 mass spectrometer, or an Agilent 1200 HPLC quipped with DAD/ELSD and G6110 MSD using one of the following conditions: 1) Ascentis Express C18 (3 x 50 mm) 2.7μm column using mobile phase containing A: 0.05% Trifluoroacetic acid in water and B: 0.05% Trifluoroacetic acid in acetonitrile with a gradient from 90:10 (A:B) to 5:95 (A:B) over 6 min at a flow rate of 1.8 mL/min, UV detection at 210 nm; 2) Aquity BEH C18, (1.0 x 50 mm) 1.7 μm column using mobile phase containing A: 0.05% Trifluoroacetic acid in water and B: 0.05% Trifluoroacetic acid in acetonitrile with a gradient from 90:10 (A:B) to 5:95 (A:B) over 2 min at a flow rate of 0.3 mL/min, UV detection at 215 nm; 3) Agilent YMC J'Sphere H-80 (3 x 50 mm) 5μm column using mobile phase containing A: 0.1% Trifluoroacetic acid in water and B: acetonitrile with a gradient from 95:5 (A:B) to 0:100 (A:B) over 3.6 min and 0:100 (A:B) for 0.4 min at a flow rate of 1.4 mL/min, UV detection at 254 and 220 nm and Agilent 1100 quadrupole mass spectrometer; 4) an Agilent TC-C18 (2.1 x 50 mm) 5μm column using mobile phase containing A: 0.0375% Trifluoroacetic acid in water and B: 0.01875% Trifluoroacetic acid in acetonitrile with a gradient from 90:10 (A:B) for 0.4 min to 90:10 to 0:100 (A:B) over 3 min and 10:90 (A:B) for 0.6 min at a flow rate of 0.8 mL/min, UV detection at 254 and 220 nm and Agilent 6110 quadrupole mass spectrometer.

Preparative HPLC purifications were usually performed using either a mass spectrometry directed system or a non-mass guided system. Usually they were performed on a Waters Chromatography Workstation configured with LC-MS System consisting of: Waters ZQ™ single quad MS system with Electrospray Ionization, Waters 2525 Gradient Pump, Waters 2767 Injecto /Collector, Waters 996 PDA Detector, the MS Conditions of: 150-750 amu, Positive Electrospray,

Collection Triggered by MS, and a Waters SUNFIRE® C-18 5 micron, 30 mm (id) x 100 mm column. The mobile phases consisted of mixtures of acetonitrile (10-100%) in water containing 0.1% TFA. Flow rates were maintained at 50 mL/min, the injection volume was 1800 μ L, and the UV detection range was 210–400 nm. An alternate preparative HPLC system used was a Gilson Workstation consisting of: Gilson GX-281 Injector/Collector, Gilson UV/VIS-155 Detector, Gilson 333 and 334 Pumps, and equipped with a column selected from the following: Phenomenex Synergi C18 (150mm x 30mm x 4 micron), YMC-Actus Pro C18 (150mm x 30mm x 5 micron), Xtimate C18 (150mm x 25mm x 5 micron), Boston Green ODS (150mm x 30mm x 5 micron), XSELECT C18 (150mm x 30mm x 5 micron), and Waters XSELECT C18 (150mm x 30mm x 5 micron). Conditions included either high pH (0-100% acetonitrile/water eluent comprising 0.1% v/v 10mM NH_4HCO_3 or 0.05% NH_4OH) or low pH (0-95% acetonitrile/water eluent comprising 0.1% v/v TFA). The injection volume ranged from 1000-8000 μ L, and the UV detection range was 210–400 nm. Mobile phase gradients were optimized for the individual compounds.

Flash chromatography was usually performed using either a Biotage® Flash Chromatography apparatus (Dyax Corp.), an ISCO CombiFlash® Rf apparatus, or an ISCO CombiFlash® Companion XL on silica gel (32-63 μ m, 60 Å pore size) in pre-packed cartridges of the size noted.

SFC chiral resolution was carried out on a Sepiate Prep SFC 100, Multigram II (MG II), THAR80 prep SFC, or a Waters SFC (80, 200, or 350) using the following conditions: Chiral Method A: AD-H column, 15% ethanol/ CO_2 ; Chiral Method B: AD-H column, 20% IPA/ CO_2 ; Chiral Method C: AS-H column, 20% MeOH/ CO_2 ; Chiral Method D: AD-H column, 20% ethanol/ CO_2 ; Chiral Method E: Lux Cellulose-4 column, 30% ethanol/ CO_2 ; Chiral Method F: IA column, 15% ethanol/ CO_2 ; Chiral Method G: IA column, 40% methanol/ CO_2 ; Chiral Method H: AD-H column, 10% methanol/ CO_2 ; Chiral Method I: AD-H column, 30% ethanol/ CO_2 ; Chiral Method J: AD-H column, 40% ethanol/ CO_2 ; and Chiral Method K: IG column, 12% methanol/ CO_2 . Chiral analytical chromatography was most commonly performed on one of CHIRALPAK® AS, CHIRALPAK® AD, CHIRALCEL® OD, CHIRALCEL® IA, or CHIRALCEL® OJ columns (250x4.6 mm) (Daicel Chemical Industries, Ltd.) with noted percentage of either ethanol in hexane (%Et/Hex) or isopropanol in heptane (%IPA/Hep) as isocratic solvent systems. Chiral preparative chromatography was conducted on one of of

CHIRALPAK AS, of CHIRALPAK AD, CHIRALCEL[®] OD, CHIRALCEL[®] IA, CHIRALCEL[®] OJ columns (20x250 mm) (Daicel Chemical Industries, Ltd.) with desired isocratic solvent systems identified on chiral analytical chromatography or by supercritical fluid (SFC) conditions.

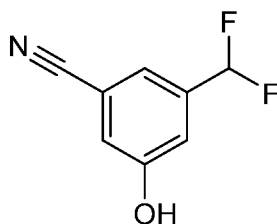
Proton or ¹H NMR was acquired using a Varian Unity-Inova 400 MHz NMR
5 spectrometer equipped with a Varian 400 ATB PFG 5mm, Nalorac DBG 400-5 or a Nalorac IDG 400-5 probe, a Varian-400MHz MR spectrometer equipped with an Auto X ID PFG Probe 5mm, a Varian 400MHz VNMRS spectrometer equipped with a PFG 4Nuc Probe 5 mm, or a Bruker AvanceIII 500MHz spectrometer equipped with a PABBO Probe 5 mm in accordance with standard analytical techniques, unless specified otherwise, and results of spectral analysis are
10 reported. ¹H NMR spectra were acquired in CDCl₃ solutions unless otherwise noted. Chemical shifts were reported in parts per million (ppm). Tetramethylsilane (TMS) was used as internal reference in CD₃Cl solutions, and residual CH₃OH peak or TMS was used as internal reference in CD₃OD solutions. Coupling constants (J) were reported in hertz (Hz).

It is understood that a chiral center in a compound may exist in the "*S*" or "*R*" stereo-
15 configuration, or as a mixture of both. Within a molecule, each bond drawn as a straight line from a chiral center encompasses each of the (*R*) and (*S*) stereoisomers as well as mixtures thereof unless otherwise noted. The compounds in **Examples 17, 18, 28-36, 43, 44, 53 and 54** contain a chiral center. The isomer mixture made in each of **Examples 17, 18, 28-36, 43, 44, 53 and 54** was separated, providing one or both of an isomer A (the faster eluting isomer) and an
20 isomer B (the slower eluting isomer), based on their observed elution order resulting from the separation as performed in the Example. Elution time and/or order of separated isomers may differ if performed under conditions different than those employed herein. Absolute stereochemistry (*R* or *S*) of the chiral center in each of the "A" and/or "B" separated stereoisomers in Examples **17, 18, 28-36, 43, 44, 53 and 54** was not determined, and "A" and "B"
25 only refer to elution order resulting from the purification conditions as performed. An asterisk (*) may be used in the associated chemical structure drawings of the Example compounds to indicate a chiral center.

Ex.	Purification conditions
17	SFC Chiralpak IC-H, 250×30 mm id, 5 μm, IPA/CO ₂ = 45%, 80 mL/min.
18	SFC Chiralpak IC-H, 250×30 mm id, 5 μm, EtOH/CO ₂ = 45%, 80 mL/min.
32	SFC Chiralpak IC-H, 250×30 mm id, 5 μm, IPA/CO ₂ = 30%, 60 mL/min.
33	SFC Chiralpak IC-H, 250×30 mm id, 5 μm, IPA/CO ₂ = 30%, 60 mL/min.
34	SFC Chiralpak IC-H, 250×30 mm id, 5 μm, IPA/CO ₂ = 45%, 73 mL/min.
35	SFC Chiralpak IC-H, 250×30 mm id, 5 μm, IPA/CO ₂ = 20%, 60 mL/min.
36	SFC Chiralpak IC-H, 250×30 mm id, 5 μm, IPA/CO ₂ = 20%, 60 mL/min.

Intermediate A Section

INTERMEDIATE A01



5 3-(difluoromethyl)-5-hydroxybenzonitrile

Step 1: 3-chloro-5-((4-methoxybenzyl)oxy)benzonitrile

To a solution of 3-chloro-5-hydroxybenzonitrile (30 g, 0.20 mol) in ACN (300 mL) was added PMBCl (34 g, 0.21 mol) and K₂CO₃ (55 g, 0.4 mmol), then the mixture was stirred at 70 °C for 4 h. The reaction mixture was filtered and concentrated in vacuum. The residue was purified by flash chromatography on silica (2% EtOAc/P.E.) to afford the title compound. ¹H NMR (400 MHz, CDCl₃): δ 7.33 (d, *J*= 8.0 Hz, 2H), 7.23 (s, 1H), 7.19 (s, 1H), 7.11 (s, 1H), 6.94 (d, *J*= 8.0 Hz, 2H), 5.00 (s, 2H), 3.83(s, 3H).

Step 2: 3-((4-methoxybenzyl)oxy)-5-vinylbenzonitrile

To a solution of 3-chloro-5-((4-methoxybenzyl)oxy)benzonitrile (50 g, 0.18 mol) in dioxane/H₂O (400 mL/80 mL) was added potassium vinyltrifluoroborate (25 g, 0.18 mol), K₂CO₃ (50 g, 0.36 mol), X-Phos (17 g, 36 mmol) and Pd(OAc)₂ (4.1 g, 18 mmol) under N₂ atmosphere, the mixture was stirred at 80 °C for 2 h. After cooled to RT, the resulting mixture was filtered

and extracted with EtOAc (3×400 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica (1-2% EtOAc/P.E.) to afford the title compound. ^1H NMR (400 MHz, CDCl_3): δ 7.34 (d, $J = 8.4$ Hz, 2H), 7.28 (s, 1H), 7.20 (s, 1H), 7.09 (s, 1H), 6.93 (d, $J = 8.4$ Hz, 2H), 6.63 (dd, $J = 17.6, 12.0$ Hz, 1H), 5.78 (d, $J = 17.6$ Hz, 1H), 5.38 (d, $J = 12.0$ Hz, 1H), 5.01 (s, 2H), 3.82 (s, 3H).

Step 3: 3-formyl-5-((4-methoxybenzyl)oxy)benzonitrile

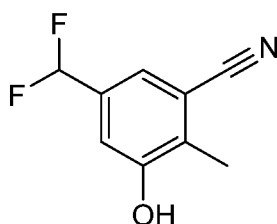
To a stirred solution of compound 3-((4-methoxybenzyl)oxy)-5-vinylbenzonitrile (28 g, 0.1 mol) in dioxane/ H_2O (180 mL / 60 mL) was added 2,6-lutidine (22 g, 0.2 mol), OsO_4 (1.3 g, 5 mmol) and NaIO_4 (43 g, 0.2 mol), the mixture was stirred at RT for 3 h. Upon reaction completion, the mixture was diluted with water, extracted with EtOAc (3×200 mL). The organic layer was washed with water and brine, dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica (2-10% EtOAc/P.E.) to afford the title compound. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 9.95 (s, 1H), 7.90 (s, 1H), 7.82 (s, 1H), 7.76 (s, 1H), 7.37 (d, $J = 8.4$ Hz, 2H), 6.93 (d, $J = 8.4$ Hz, 2H), 5.14 (s, 2H), 3.73 (s, 3H).

Step 4: 3-(difluoromethyl)-5-((4-methoxybenzyl)oxy)benzonitrile

To a stirred solution of 3-formyl-5-((4-methoxybenzyl)oxy)benzonitrile (22 g, 82 mmol) in DCM (250 mL) was added DAST (106 g, 0.6 mol) at 0°C under N_2 atmosphere, then the mixture was stirred for 3 h at RT. Upon reaction completion, the mixture was quenched with water, extracted with DCM (3×200 mL). The organic layer was washed with water and brine, dried over Na_2SO_4 , filtered and concentrated under reduce pressure to give the title compound.

Step 5: 3-(difluoromethyl)-5-hydroxybenzonitrile

A solution of 3-(difluoromethyl)-5-((4-methoxybenzyl)oxy)benzonitrile (23.7 g, 82 mmol) in TFA/TFAA (100 mL/ 50 mL) was stirred at 110°C for 3 h. When reaction was complete, the resulting mixture was quenched with saturated NaHCO_3 aq. (100 mL) and extracted with EtOAc (3×150 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 , filtered and concentrated under reduced pressure to afford the title compound. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 10.66 (s, 1H), 7.41 (s, 1H), 7.28 (s, 1H), 7.23 (s, 1H), 6.97 (t, $J = 56.0$ Hz, 1H).

INTERMEDIATE A02**Step 1: 5-formyl-2-methylbenzonitrile**

Into a 20-L 4-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed a solution of 5-bromo-2-methylbenzonitrile (750 g, 38.26 mol) in tetrahydrofuran (6 L), n-BuLi (1.54 L, 38.26 mol) was added dropwise at -78 °C, the resulting solution was stirred for 30 min, the N,N-dimethylformamide (295 g, 4.04 mol, 1.05 equiv) was added dropwise. The reaction mixture was then stirred at -78 °C for 30 min in a liquid nitrogen bath, and then quenched by the addition of saturated NH₄Cl aq. (5 L). The resulting solution was extracted with EtOAc (3 × 5 L). The organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give the title compound.

Step 2: 3-bromo-5-formyl-2-methylbenzamide

Into a 3-L 4-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed a solution of 5-formyl-2-methylbenzonitrile (245 g, 1.69 mol) in sulfuric acid (980 mL), the reaction mixture was stirred at 60 °C, 1-bromopyrrolidine-2,5-dione (300 g, 1.69 mol) was added in 3 batches. The resulting solution was stirred at 60 °C for 30 min. The reaction was then quenched by the addition of 5 L of water/ice, and stirred for 1 h. The solids were collected by filtration and dried under vacuum to afford the title compound and used as is in the next step.

Step 3: 3-bromo-5-formyl-2-methylbenzonitrile

Into a 20-L 4-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed a solution of 3-bromo-5-formyl-2-methylbenzamide (500 g, 2.07 mol) in dichloromethane (10 L), pyridine (524.5 g, 6.63 mol). While the resulting solution was stirred at 0 °C, the 2,2,2-trifluoroacetate (1305 g, 6.21 mol) was added dropwise. The resulting solution was stirred for 30 min at RT, then quenched with water/ice (5 L), and extracted with DCM (3 × 5 L). The organic layers were combined and dried over anhydrous Na₂SO₄, filtered and

concentrated under reduced pressure. The residue was purified with flash chromatography on silica (20% EtOAc/hexanes) to afford the title compound.

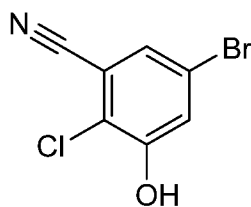
Step 4: 3-bromo-5-(difluoromethyl)-2-methylbenzonitrile

To a solution of 3-bromo-5-formyl-2-methylbenzonitrile (360 g, 1.61 mol) in dichloromethane (5.4 L), DAST (260 g, 1.61 mol, 1.00 equiv) was added dropwise at RT. The resulting solution was stirred at RT for 1 h, and then quenched with water/ice (3 L). The resulting solution was extracted with DCM (3 × 5 L). The organic layers were combined and dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford the title compound and used as is in the following step.

Step 5: 5-(difluoromethyl)-3-hydroxy-2-methylbenzonitrile

To a solution of 3-bromo-5-(difluoromethyl)-2-methylbenzonitrile (320 g, 1.30 mol) in 1,4-dioxane (1.6 L), was added solution of KOH (146 g, 2.60 mol) in water (1.6 L), Pd₂(dba)₃ (67 g, 64.92 mmol), and 2-di-tert-butylphosphino-2',4',6'-triisopropylbiphenyl (55 g, 129.53 mmol). The resulting mixture was purged by nitrogen (3×) and stirred at 90 ° C for 1 h, and then partitioned between ice water (4 L) and EtOAc (3× 2 L). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified with flash chromatography on silica (33% EtOAc/hexanes) to afford the title compound. MS: 182 (M+1). ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.65 (s, 1H), 7.42 (d, J = 1.6 Hz, 1H), 7.26 (d, J = 1.5 Hz, 1H), 6.99 (s, 1H), 2.34 (d, J = 1.3 Hz, 3H).

INTERMEDIATE A03



5-bromo-2-chloro-3-hydroxybenzonitrile

Step 1: 2-amino-5-bromo-3-fluorobenzonitrile

To a stirred solution of 2-amino-3-fluorobenzonitrile (10 g, 73.5 mmol) in DMF (10 mL) was added NBS (13.07 g, 73.5 mmol) and the resulting mixture was stirred at 0 °C for 12 h. Upon the reaction completion, the reaction mixture was diluted with water (50 mL). And the precipitate formed was removed by filtration, and the filtrate was concentrated under reduced

pressure to give the title compound. MS: 215 and 217 (M+1).

Step 2: 5-bromo-2-chloro-3-fluorobenzonitrile

To a mixture of 2-amino-5-bromo-3-fluorobenzonitrile (9 g, 41.9 mmol), copper(I) chloride (12.43 g, 126 mmol) and copper(II) chloride (19.70 g, 146 mmol) in ACN (80 mL),
5 was added tert-butyl nitrite (19.91 mL, 167 mmol) at 0°C. The resulting mixture was stirred at 25°C for 6 h. The mixture was diluted with water (150 mL) and extracted with EtOAc (3 × 100 mL). The organic layer was washed with brine (3 × 50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica (10-100% EtOAc/P.E.) to give the title compound.

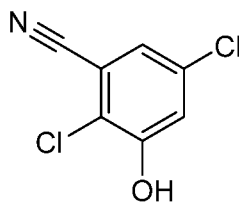
10 Step 3: 5-bromo-2-chloro-3-((4-methoxybenzyl)oxy)benzonitrile

To a stirred solution of (4-methoxyphenyl)methanol (2.475 g, 17.91 mmol) in DMF (100 mL) was added NaH (0.931 g, 23.29 mmol) at 0°C. After stirring for 20 min, was added 5-bromo-2-chloro-3-fluorobenzonitrile (4.2 g, 17.91 mmol). The reaction mixture was stirred at 25 °C for 3 h, then partitioned between water (50 mL) and EtOAc (3 × 50 mL). The organic
15 layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica (15 -100% EtOAc/P.E.) to afford the title compound.

Step 4: 5-bromo-2-chloro-3-hydroxybenzonitrile

To a stirred solution of 5-bromo-2-chloro-3-((4-methoxybenzyl)oxy)benzonitrile (3.5 g, 9.93 mmol) in TFA (10 mL) and DCM (50 mL) was stirred at 25 °C for 3 h. Upon reaction
20 completion, the mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on silica (15 -100% EtOAc/P.E.) to afford the title compound.

INTERMEDIATE A04



25 2,5-dichloro-3-hydroxybenzonitrile

Step 1: 2-amino-5-bromo-3-fluorobenzonitrile

To a stirred solution of 2-amino-3-fluorobenzonitrile (5 g, 36.7 mmol) in DMF (50 mL) was added 1-chloropyrrolidine-2,5-dione (5.15 g, 38.6 mmol) and the resulting mixture was stirred at 60 °C for 6 h. The mixture was partitioned between water (200 mL) and EtOAc (2×150 mL). The combined organic layers were washed with brine (3×300 mL), dried with anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give the title compound, which was used for the next step without purification. MS: 171.1 (M+1).

Step 2: 2,5-dichloro-3-fluorobenzonitrile

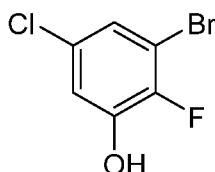
To a mixture of 2-amino-5-chloro-3-fluorobenzonitrile (6.217 g, 36.4 mmol), copper(I) chloride (10.82 g, 109 mmol) and copper(II) chloride (17.15 g, 128 mmol) in ACN (60 mL), was added tert-butyl nitrite (17.34 mL, 146 mmol) at 25°C for 1 h. The reaction mixture was diluted with water (180 mL) and extracted with EtOAc (3 × 120 mL). The organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica (10 - 100% EtOAc/P.E.) to afford the title compound. ¹H NMR (400 MHz, chloroform-*d*): δ 7.51 (dd, *J*=2.26, 1.65 Hz, 1 H), 7.44 - 7.47 (m, 1 H).

Step 3: 2,5-dichloro-3-((4-methoxybenzyl)oxy)benzonitrile

To a stirred solution of (4-methoxyphenyl)methanol (2.75 g, 19.89 mmol) in DMF (40 mL) was added NaH (1.034 g, 25.9 mmol) at 0°C. The mixture was stirred at 0°C for 30 min, then was added 2,5-dichloro-3-fluorobenzonitrile (3.78 g, 19.89 mmol), and then stirred at 25 °C for 2 h. The reaction mixture was diluted with water (200 mL) and extracted with EtOAc (3 × 150 mL). The organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated to give the title compound. MS: 308.1 (M+1).

Step 4: 2,5-dichloro-3-hydroxybenzonitrile

To a stirred solution of 2,5-dichloro-3-((4-methoxybenzyl)oxy)benzonitrile (6.13 g, 19.89 mmol) in DCM (60 mL), TFA (20 mL) was added and then stirred at 25 °C for 1 h. Upon the completion, the reaction mixture was poured into sat. NaHCO₃ aq. (30 mL), extracted with DCM (3 × 60 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give the title compound, which was used directly without further purification. MS: 187.9 (M-1).

INTERMEDIATE A053-bromo-5-chloro-2-fluorophenolStep 1: 2-(3-bromo-5-chloro-2-fluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

5 To a solution of 2-bromo-4-chloro-1-fluorobenzene (300 g, 1.43 mol) in hexane (4.5 L), was added B₂Pin₂ (363.7 g, 1.43 mol), Ir [(Ome)(1,5-COD)]₂ (14.2 g, 21.42 mmol), 4-tert-butyl-2-(4-tert-butylpyridin-2-yl)pyridine (11.5 g, 42.85 mmol) after it was purged with nitrogen three times. The resulting solution was stirred at RT overnight and then concentrated under vacuum. The residue was purified by flash chromatography on silica (0-100% EtOAc/P.E.) to obtain the

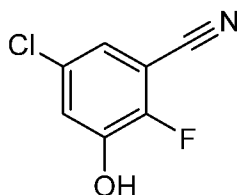
10 title compound.

Step 2: 3-bromo-5-chloro-2-fluorophenol

To a solution of 2-(3-bromo-5-chloro-2-fluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (385 g, 1.15 mol) in THF (3.85 L), was added a solution of sodium hydroxide (138 g, 3.45 mol) in water (3 L), 35% hydrogen peroxide aq. (390 g, 3.44 mol) at 0°C. The

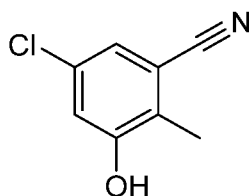
15 resulting solution was stirred at 0 °C for 2 h, and quenched by with sat. Na₂S₂O₃ aqueous solution. After the pH of the solution was adjusted to 3-4 with HCl (1 M), the resulting solution was extracted with EtOAc (3 × 3 L). The combined organic layers were washed with brine, then concentrated under reduced pressure. The residue was purified by flash chromatography on silica (0 – 90% EtOAc/P.E.) to afford the title compound. ¹H NMR (400 MHz, CDCl₃): δ 11.31

20 (br. s., 1H), 7.47 (dd, *J* = 2.4, 4.4 Hz, 1H), 7.30 (dd, *J* = 2.4, 7.6 Hz, 1H).

INTERMEDIATE A065-chloro-2-fluoro-3-hydroxybenzonitrile

To a solution of 3-bromo-5-chloro-2-fluorophenol (86 g, 343 mmol) in NMP (860 mL), was added CuCN (154 g, 1.72 mol, 5.0 *eq*) in one portion. The resulting reaction mixture was stirred at 180 °C for 2 h, then partitioned between ice water (1 L) and EtOAc (3 × 800 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica (2 - 33% EtOAc/P.E.) to afford the title compound. ¹H NMR (400 MHz, DMSO-*d*₆): δ 11.33 (br. s., 1H), 7.49 (dd, *J* = 2.5, 4.5 Hz, 1H), 7.30 (dd, *J* = 2.5, 7.6 Hz, 1H).

INTERMEDIATE A07



5-chloro-3-hydroxy-2-methylbenzonitrile

Step 1: 2,3-difluorobenzaldehyde

To a solution of 1,2-difluorobenzene (1668 g, 14.62 mol) in THF (16.7 L) cooled at -78 °C, was added a THF solution of *n*-Buli (6.44 L, 16.08 mol) dropwise with stirring over 60 min. Then to this mixture, was added *N,N*-dimethylformamide (5340 g, 73.06 mol) dropwise with stirring at -78 °C over 60 min. The resulting solution was stirred at -78 °C for 1h. The reaction was then quenched with saturated NH₄Cl aq. (10 L), then extracted with EtOAc (3 × 10 L). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica (2% EtOAc/P.E.) to afford the title compound.

Step 2: (E)-N-[(2,3-difluorophenyl)methylidene]hydroxylamine

A mixture of 2,3-difluorobenzaldehyde (2410 g, 16.96 mol) in a 70% solution of NH₂OH (672 g, 20.35 mol) in DMF (10 L) was stirred at 20 °C for 3 h, then partitioned between water (6 L) and EtOAc (3 × 8 L). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica (2% EtOAc/P.E.) to afford the title compound.

Step 3: 2,3-difluorobenzonitrile

A solution of (*E*)-*N*-[(2,3-difluorophenyl)methylidene]hydroxylamine (2025 g, 12.89 mol) in DMF (11 L) was treated with POCl₃ (5688 g, 37.10 mol). The resulting solution was stirred at 25°C for 3 h, then partitioned between water (6 L) and EtOAc (3 × 6 L). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica (2% EtOAc/P.E.) to afford the title compound.

Step 4: 2-amino-3-fluorobenzonitrile

In a seal reactor, a solution of 2,3-difluorobenzonitrile (1273 g, 9.15 mol) in EtOH (13 L) was bubbled in NH₃(gas). The resulting solution was stirred at 140°C for 8 h, cooled to RT then concentrated under reduced pressure. The residue was partitioned between water (5 L) and MTBE (3 × 8L). The combined organic layers were washed with water, brine and dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford the title compound.

Step 5: 2-amino-5-chloro-3-fluorobenzonitrile

A solution of 2-amino-3-fluorobenzonitrile (934 g, 6.86 mol) in DMF (14 L) was treated with NCS (1008 g, 7.55 mol). The resulting solution was stirred at 45°C for 2 h, then partitioned between ice water (20 L) and EtOAc (3 × 12 L). The organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica (3% EtOAc/P.E.) to afford the title compound.

Step 6: 2-bromo-5-chloro-3-fluorobenzonitrile

To a mixture of *t*-BuONO (815 g, 7.88 mol) and CuBr₂ (1365 g, 6.13 mol) in ACN (8 L), was added a solution of 2-amino-5-chloro-3-fluorobenzonitrile (747 g, 4.38 mol) in ACN (7 L) dropwise with stirring over 90 min. The resulting mixture was stirred at RT for 10 h, and diluted with water (15 L), and then extracted with EtOAc (3 × 10 L). The organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica (3% EtOAc/P.E.) to afford the title compound.

Step 7: 5-chloro-3-fluoro-2-methylbenzonitrile

A mixture of 2-bromo-5-chloro-3-fluorobenzonitrile (768 g, 3.28 mol), 1,4-methylboronic acid (297 g, 4.96 mol), potassium carbonate (913 g, 6.61 mol) and PdCl₂(dppf) (213 g, 0.33 mol) in degassed 1,4-dioxane (4500 mL) and water (450 mL) was stirred at 100°C for 60 min, and then diluted with water (4L), and extracted with EtOAc (3 × 6 L). The organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica (3% EtOAc/P.E.) to afford the title compound.

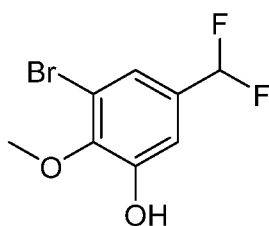
Step 8: 5-chloro-3-[(4-methoxyphenyl)methoxy]-2-methylbenzonitrile

Under atmosphere of nitrogen, to a solution of 4-Methoxybenzyl alcohol (410 g, 2.97mol) in DMF (3200 mL), was added sodium hydride (128 g, 5.33 mol), followed by addition of a solution of 5-chloro-3-fluoro-2-methylbenzonitrile (418 g, 2.46 mol) in DMF (800 mL) drop wise. The resulting solution was stirred at 25°C for 12 h, then diluted with ice water (2 L), and extracted with EtOAc (3 × 3L). The organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting solid was washed with petroleum ether and collected on top of a filter to afford the title compound.

Step 9: 5-chloro-3-hydroxy-2-methylbenzonitrile

A solution of 5-chloro-3-[(4-methoxyphenyl)methoxy]-2-methylbenzonitrile (518 g, 1.80 mol) in DCM (1500 mL) was treated with TFA (500 mL). The resulting solution was stirred at 25°C for 1 h. The solids were collected on top of a filter to afford the title compound. MS: 166 (M-1). ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.67 (s, 1H), 7.32-7.33 (d, 1H), 7.07-7.08 (d, 1H), 2.24 (s, 3H).

INTERMEDIATE A08



3-bromo-5-(difluoromethyl)-2-methoxyphenol

Step 1: 3-bromo-4,5-dihydroxybenzaldehyde

To a solution of 3-bromo-4-hydroxy-5-methoxybenzaldehyde (10 g, 43.3 mmol) in DCM (100 mL) was added a solution of BBr₃ (9.00 mL, 95 mmol) in DCM (100 mL) at 0 °C, then the reaction mixture was stirred at 0 °C for 20 min and 25 °C for 2.5 h. Upon completion, the reaction was quenched by slow addition of MeOH (50 mL). The solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica (0-20%, MeOH/DCM) to afford the title compound. MS: 216.9 (M+1).

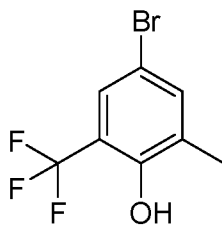
Step 2: -bromo-5-hydroxy-4-methoxybenzaldehyde

To a solution of 3-bromo-4,5-dihydroxybenzaldehyde (6 g, 27.6 mmol) in DMF (80 mL) was added lithium carbonate (4.09 g, 55.3 mmol). After stirring at 45 °C for 1 h, the reaction mixture was treated with MeI (2.59 mL, 41.5 mmol). The reaction mixture was stirred at 45 °C for another 2 h, and then poured into ice water (400 mL), adjusted pH ~ 6 with 1 N HCl, extracted with EtOAc (3×150 mL). The organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica (5 – 33% EtOAc/P.E.) to afford the title compound. MS: 231.0 (M+1).

Step 3: 3-bromo-5-(difluoromethyl)-2-methoxyphenol

To a solution of 3-bromo-5-hydroxy-4-methoxybenzaldehyde (3.23 g, 13.98 mmol) in DCM (30 mL) was added DAST (18.47 mL, 140 mmol). The reaction mixture was stirred at 20 °C for 1 h, and then quenched by slow addition of sat. NaHCO₃ aq. (100 mL), extracted with DCM (3×50 mL). The organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica (3-25% EtOAc/P.E.) to give the title compound. MS: 253.8 (M+1).

INTERMEDIATE A09



4-bromo-2-methyl-6-(trifluoromethyl)phenol

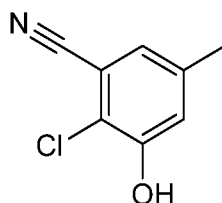
Step 1: 4-bromo-2-iodo-6-(trifluoromethyl)phenol

A solution of 4-bromo-2-(trifluoromethyl)phenol (4 g, 16.60 mmol), KI (16 g, 96 mmol) and I₂ (8.5 g, 33.5 mmol) in water (50 mL) was treated with NH₃/H₂O (200 mL), and stirred at 30 °C for 16 h. Upon completion, the reaction mixture was neutralized with HCl (6 M) to pH of 7, then the precipitate was collected on top of a filter to afford the title compound. MS: 366.7 (M+1).

Step 2: 4-bromo-2-methyl-6-(trifluoromethyl)phenol

To a solution of 4-bromo-2-iodo-6-(trifluoromethyl)phenol (5 g, 13.63 mmol) in NMP (10 mL) was added Pd₂(dba)₃ (0.374 g, 0.409 mmol), triphenylphosphine (0.715 g, 2.73 mmol). The mixture was purged with N₂ and heated at 50 °C for 10 min, followed by addition of copper(I) iodide (0.260 g, 1.363 mmol). After the mixture was heated at 50 °C for another 10 min, tetramethylstannane (3.66 g, 20.44 mmol) was added into the reaction, and it was heated to 120 °C for 3 h. Upon complete conversion, the mixture was diluted with sat. KF aq. (50 mL) and extracted with EtOAc (3×40 mL). The organic layer was washed with water and brine, dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by reverse phase HPLC (ACN/water with 0.1% TFA modifier) to give the title compound. MS: 255 (M+1).

INTERMEDIATE A10



2-chloro-3-hydroxy-5-methylbenzonitrile

Step 1: 2-chloro-3-((4-methoxybenzyl)oxy)-5-methylbenzonitrile

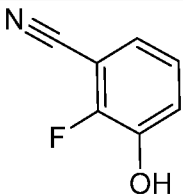
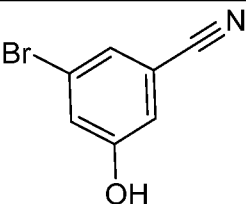
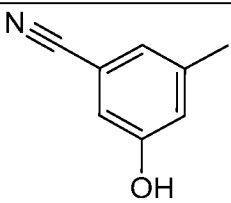
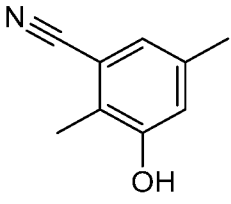
To a solution of 5-bromo-2-chloro-3-((4-methoxybenzyl)oxy)benzonitrile (see Step 3 of Intermediate A03) (0.350 g, 0.993 mmol) in 1,4-dioxane (10 mL) was added K₂CO₃ (0.274 g, 1.985 mmol) and H₂O (1 mL), was added methylboronic acid (0.059 g, 0.993 mmol) and 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (0.081 g, 0.099 mmol). The resulting mixture was heated at 80 °C for 16 h, and then quenched with water and extracted with EtOAc. The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica (P.E. 100%) to afford the title compound.

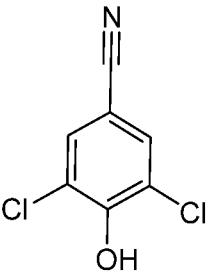
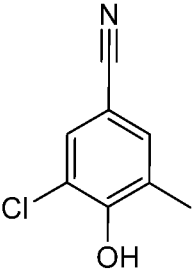
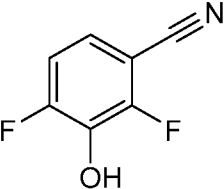
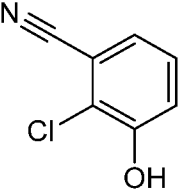
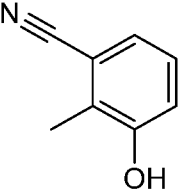
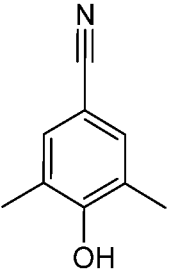
Step 2: 2-chloro-3-hydroxy-5-methylbenzonitrile

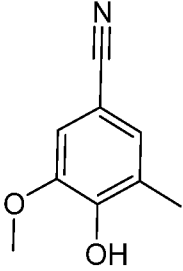
To a solution of 2-chloro-3-((4-methoxybenzyl)oxy)-5-methylbenzonitrile (0.185 g, 0.643 mmol) in DCM (20 mL) was added TFA (0.050 ml, 0.643 mmol) at 0°C. The resulting mixture was stirred at RT for 2 h, and then was concentrated under reduced pressure. The residue
 5 was purified by flash chromatography on silica (EtOAc/P.E. = 0-20%) to afford the title compound. MS: 168.0 (M+1).

The following intermediates in Table 1 were purchased from commercial sources.

TABLE 1

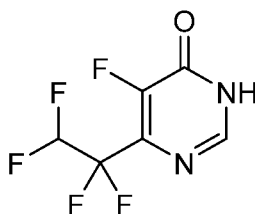
INT	Structure	IUPAC Name	CAS#
A11		2-fluoro-3-hydroxybenzonitrile	1000339-24-1
A12		3-bromo-5-hydroxybenzonitrile	770718-92-8
A13		3-hydroxy-5-methylbenzonitrile	95658-81-4
A14		2,5-dimethyl-3-hydroxybenzonitrile	90563-55-6

A15		3,5-dichloro-4-hydroxybenzonitrile	1891-95-8
A16		3-chloro-4-hydroxy-5-methylbenzonitrile	173900-45-3
A17		2,4-difluoro-3-hydroxybenzonitrile	1214373-88-2
A18		2-chloro-3-hydroxybenzonitrile	51786-11-9
A19		3-hydroxy-2-methylbenzonitrile	55289-04-8
A20		4-hydroxy-3,5-dimethylbenzonitrile	4198-90-7

A21		4-hydroxy-3-methoxy-5-methylbenzonitrile	173900-47-5
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Intermediate B Section

INTERMEDIATE B01



5 5-fluoro-6-(1,1,2,2-tetrafluoroethyl)-3,4-dihydropyrimidin-4-one

Step 1: 2,2,3,3-tetrafluoropropanoic acid

To a solution of potassium heptaoxidichromium (1782 g, 6.06 mol) in sulfuric acid (2097 g, 21.38 mol) and water(2400 mL), was added of 2,2,3,3-tetrafluoropropan-1-ol (800 g, 6.06 mol) dropwise with stirring at 100 °C. The resulting solution was stirred at 100 °C for 5 h with refluxing, and then extracted with MTBE (4×2L). The organic layer was dried with anhydrous sodium sulfate and concentrated under reduced pressure to afford the title compound and used as is for the next step.

Step 2: 2,2,3,3-tetrafluoro-N-methoxy-N-methylpropanamide

To a solution of 2,2,3,3-tetrafluoropropanoic acid (crude product from previous step, 45% purity, 1007g, 3.15 mol) in THF (4600 mL), was added sulfurooyl dichloride (787.2 g, 6.62 mol) dropwise at 0°C, followed by dropwise addition of DMF (753.4 g, 10.31 mol). After being stirred at RT for 45 min, the reaction mixture was cooled to 0°C , and then treated with methoxy(methyl)amine hydrochloride (1222.5 g, 12.53 mol), and TEA (1913 g, 18.91 mol) dropwise. The resulting mixture was stirred at RT for 5 h, and then quenched with ice water (2 L), and extracted with MTBE (3 L). The organic layer was washed with sat. NaHCO₃ aq, brine, dried over anhydrous sodium sulfate, filtered and distilled to afford the title compound.

Step 3: Ethyl 2,4,4,5,5-pentafluoro-3-oxopentanoate

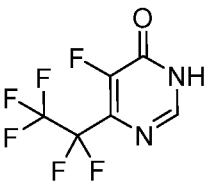
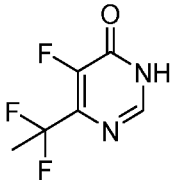
To a solution of 2,2,3,3-tetrafluoro-N-methoxy-N-methylpropanamide (470 g, 2.49 mol) in THF(4700 mL), was added ethyl 2-fluoroacetate (316.2 g, 2.98 mol), 1M solution of LiHMDS in THF(3729 mL, 3.73 mol) at -78°C. The resulting mixture was stirred at -78°C for 2 h, and then quenched with sat. NH₄Cl aq (1 L). After the pH value of the solution was adjusted to 3 with HCl (1M), the reaction mixture was extracted with MTBE (3×2L). The organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the title compound, which was used for the next step directly.

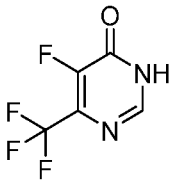
Step 4: 5-fluoro-6-(1,1,2,2-tetrafluoroethyl)-3,4-dihydropyrimidin-4-one

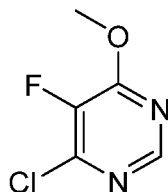
To a solution of ethyl 2,4,4,5,5-pentafluoro-3-oxopentanoate (533 g, 2.28 mol) in methanol (5330 mL), was added formamidine acetate (1185.1 g, 11.38 mol), and sodium methoxide (492 g, 9.11 mol). The resulting mixture was stirred at RT for 2 h, then quenched with ice water (1.5 L). After the pH value of the solution was adjusted to 3 with HCl(2M), the resulting mixture was extracted with MTBE (3× 1 L). The combined organic layers was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by re-crystallization from MTBE/P.E.(1:5) to afford the title compound. MS: 212.9 (M-1). ¹HNMR: (300MHz, CD₃OD): δ 8.10 (1H, s), 6.67~6.38(1H, m).

The following intermediates in Table 2 were prepared according to scheme C using the procedure outlined in the synthesis of intermediate **B01** using the relevant fluorinated alkyl alcohol or its corresponding acid/methyl ester.

TABLE 2

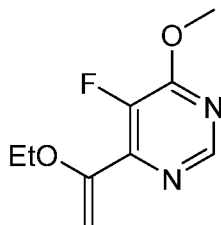
INT	Structure	IUPAC Name	MS (M+1)
B02		5-fluoro-6-(pentafluoroethyl)-3,4-dihydropyrimidin-4-one	231.0 (M-1)
B03		6-(1,1-difluoroethyl)-5-fluoropyrimidin-4(3H)-one	177.1 (M-1)

B04		5-fluoro-6-(trifluoromethyl) pyrimidin-4(3H)-one	183.0 (M+1)
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INTERMEDIATE B054-chloro-5-fluoro-6-methoxypyrimidine

5 To a solution of 4,6-dichloro-5-fluoropyrimidine (8.0 g, 47.9 mmol) in MeOH (80mL) was added sodium methoxide (3.05g, 56.5 mmol) at 0 °C. The resulting reaction mixture was stirred at 20 °C for 2 h, then quenched with water (20 mL) and then extracted with EtOAc (3×20 mL). The organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtrated and concentrated under reduced pressure to afford the title compound. MS: 163.1 (M+1). ¹H NMR

10 (400 MHz, DMSO-*d*₆): δ 8.45(s, 1H), 4.03(s, 1H).

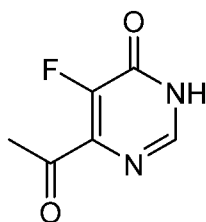
INTERMEDIATE B064-(1-ethoxyvinyl)-5-fluoro-6-methoxypyrimidine

15 To a solution of 4-chloro-5-fluoro-6-methoxypyrimidine (5.2g, 28.8 mmol), tributyl (1-ethoxyvinyl) stannane (12.48 g, 34.5 mmol) in DMF (50mL) was added Pd(Ph₃P)₄ (0.5g, 0.433 mmol) . The resulting reaction mixture was stirred at 100 °C for 4 h under N₂ atmosphere. Upon completion, the reaction was diluted with water (30 mL), extracted with EtOAc (3×100 mL). The combined organic layers were treated with sat. KF aq. (80 mL) and stirred at RT for 0.5 h, then passed through a CELITE[®] filter. The filtrate was washed with water, brine, and dried over

20 anhydrous Na₂SO₄, filtrated and concentrated under reduced pressure. The residue purified by

column chromatography on silica (10-90% EtOAc/P.E.) to afford the title compound. ¹H NMR (400 MHz, CDCl₃): δ 8.49 (s, 1H), 5.08 (d, *J* = 2.8 Hz, 1H), 4.64 (d, *J* = 3.2 Hz, 1H), 4.06(s, 3H), 3.93 (m, 2H), 1.42(m, 3H).

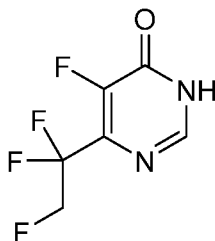
INTERMEDIATE B07



6-acetyl-5-fluoropyrimidin-4(3H)-one

To a solution of 4-(1-ethoxyvinyl)-5-fluoro-6-methoxypyrimidine (4.5 g, 20.43 mmol) in THF (30 mL) was added 6M HCl aq. (20 mL, 120 mmol) dropwise at 0 °C. The resulting reaction solution was stirred at 20 °C for 18 h, and then concentrated under reduced pressure while keeping the temperature of the bath at 40 °C to afford the title compound. ¹H NMR (400 MHz, DMSO-d₆): δ 8.15(s, 1H), 2.50(s, 3H).

INTERMEDIATE B08



5-fluoro-6-(1,1,2-trifluoroethyl)pyrimidin-4(3H)-one

Step 1: 2-fluoro-1-(5-fluoro-6-methoxypyrimidin-4-yl)ethanone

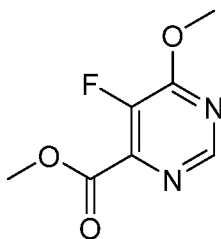
A solution of 4-(1-ethoxyvinyl)-5-fluoro-6-methoxypyrimidine, **B06** (0.2 g, 0.86 mmol) in ACN (3 mL) was added dropwise to a suspension of 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (0.456 g, 1.29 mmol) in ACN (2 mL) and water (1 mL) over 4 h, maintaining the temperature below 15 °C. The reaction mixture was then quenched with sat. NaHCO₃ aq. (10 mL) and left to stir for 10 min. After finished, the mixture was extracted with EA (3×10 mL). The combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure to afford the title compound. MS: 189.1 (M+1).

Step 2: 5-fluoro-4-methoxy-6-(1,1,2-trifluoroethyl)pyrimidine

To a solution of 2-fluoro-1-(5-fluoro-6-methoxypyrimidin-4-yl)ethanone (0.15 g, 0.60 mmol) in DCM (2 mL) was added diethylaminosulfur trifluoride (0.578 g, 3.59 mmol). The resulting reaction mixture was stirred at 20 °C for 4 h, and then diluted with water, and extracted with EtOAc (3×50 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by preparative TLC (20% EtOAc/P.E.) to afford the title compound. ¹H NMR (400MHz, CDCl₃) δ 8.56 (s, 1H), 4.99 (t, J=12.0 Hz, 1H), 4.88 (t, J=12.0 Hz, 1H), 4.12 (s, 3H).

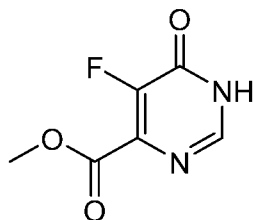
Step 3: 5-fluoro-6-(1,1,2-trifluoroethyl)pyrimidin-4(3H)-one

To a mixture of 5-fluoro-4-methoxy-6-(1,1,2-trifluoroethyl)pyrimidine (0.05 g, 0.238 mmol) and KI (0.119 g, 0.714 mmol) in ACN (15 mL), was added chlorotrimethylsilane (0.078 g, 0.714 mmol) at RT. The resulting mixture was stirred at 80 °C for 4 h, and then diluted with EtOAc, washed with aq. Na₂S₂O₃ and brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford the title compound. MS: 197.1 (M+1).

INTERMEDIATE B095-fluoro-6-methoxypyrimidine-4-carboxylate

Into a 20-L sealed tube purged with N₂, was placed a solution of 4-chloro-5-fluoro-6-methoxypyrimidine, **B05** (410 g, 2.52 mol) in MeOH (8.2 L), triethylamine (1.247 kg, 12.32 mol), PdCl₂dppf (201 g, 246.32 mmol). The solution was set up for carbonylation in a bomb with CO at 2 bar and heated at 50 °C for 16 h. The solids were filtered out. The filtrate was concentrated under reduced pressure to remove MeOH, and then diluted with EtOAc (4 L). The solids were filtered out. The filtrate was again concentrated under reduced pressure. The residue was purified with column chromatography on silica (10% EtOAc/hexanes) and then recrystallized (propan-2-ol:H₂O=2:7) to afford the title compound. MS: 187 (M+1). ¹H NMR (400MHz, CDCl₃): δ 5.587 (s, 1H), 4.109-4.075 (s, 3H), 4.003-3.935 (s, 3H).

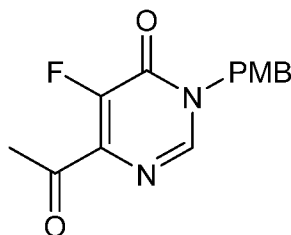
INTERMEDIATE B10



Methyl 5-fluoro-6-hydroxypyrimidine-4-carboxylate

Trimethylsilyl chloride (25.7 mL, 201 mmol) was slowly added to a stirring slurry of methyl 5-fluoro-6-methoxypyrimidine-4-carboxylate, **B09** (25 g, 134 mmol) and potassium iodide (33.4 g, 201 mmol) in ACN (300 mL) at 25 °C. The resulting mixture was stirred at 25 °C for 2 h. LC-MS indicated reaction was complete. The reaction was quenched with methanol (100 mL) and concentrated to afford the title compound, which was used in the next step without further purification. MS: 173.0 (M+1). ¹H NMR (400 MHz, DMSO-*dd6*) 8.12 (s, 1H), 2.59 (s, 3H).

INTERMEDIATE B11



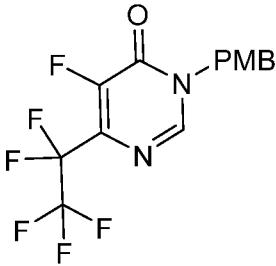
6-acetyl-5-fluoro-3-(4-methoxybenzyl)pyrimidin-4(3H)-one

To a solution of 6-acetyl-5-fluoropyrimidin-4(3H)-one, **B07** (1.0 g, 5.44 mmol) in DMF (10 mL) was added K₂CO₃ (2.257 g, 16.33 mmol). The resulting reaction mixture was stirred at 20 °C for 10 min before 1-(chloromethyl)-4-methoxybenzene (1.023 g, 6.53 mmol) was added. The reaction mixture was stirred at 20 °C for another 6 h, and then diluted with water (50 mL) and extracted with EtOAc (3×50 mL). The combined organic layers were washed with water, brine, dried over anhydrous Na₂SO₄, filtrated and concentrated under reduced pressure. The residue was purified by column chromatography on silica (50% EtOAc/P.E.) to afford the title compound. MS: 277.1 (M+1). ¹H NMR (400 MHz, CDCl₃): δ 8.01 (s, 1H), 7.29 (m, 2H), 6.89 (d, *J*=8.8, 2H), 5.09 (s, 2H), 3.81 (s, 2H), 2.58 (d, *J*=8.8, 3H).

The following intermediates in Table 3 were prepared under similar conditions as the above synthetic procedure outlined in the synthesis of intermediate **B11** using a corresponding intermediate **B** that is prepared as described in the Intermediate **B** section.

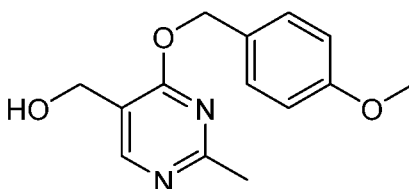
TABLE 3

INT	Structure	IUPAC Name	MS (M+1)
B12		6-(1,1-difluoroethyl)-5-fluoro-3-(4-methoxybenzyl)pyrimidin-4(3H)-one	299.0
B13		5-fluoro-3-(4-methoxybenzyl)-6-(1,1,2-trifluoroethyl)pyrimidin-4(3H)-one	317.1
B14		Methyl 5-fluoro-1-(4-methoxybenzyl)-6-oxo-1,6-dihydropyrimidine-4-carboxylate	293.0
B15		5-fluoro-3-(4-methoxybenzyl)-6-(1,1,2,2-tetrafluoroethyl)pyrimidin-4(3H)-one	335.1

B16		5-fluoro-3-(4-methoxybenzyl)-6-(perfluoroethyl)pyrimidin-4(3H)-one	353.1
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Intermediate C Section

INTERMEDIATE C01



5 [4-[(4-methoxyphenyl)methoxy]-2-methylpyrimidin-5-yl]methanol

Step 1: methyl 4-hydroxy-2-methylpyrimidine-5-carboxylate

Into a 10-L 4-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 30% solution of NaOCH₃ in MeOH(883 mL), MeOH (5 L), 1,3-diethyl 2-(ethoxymethylidene)propanedioate (350 g, 1.62 mol), ethanimidamide hydrochloride (152.3 g, 1.61 mol). The resulting mixture was heated to reflux for 16 h. The solids were collected on top of a filter to afford the title compound.

Step 2: methyl 4-[(4-methoxyphenyl)methoxy]-2-methylpyrimidine-5-carboxylate

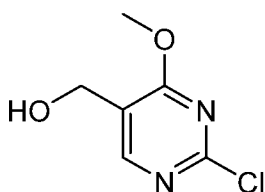
Into a 20-L 4-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed a solution of methyl 4-hydroxy-2-methylpyrimidine-5-carboxylate (340 g, 2.02 mol) in 1,4-dioxane (8 L), 1-(chloromethyl)-4-methoxybenzene (378 g, 2.42 mol), Ag₂O (655.9 g, 2.83 mol). The resulting mixture was heated to reflux for 15 h. The solids were filtered out. The filtrate was concentrated under vacuum. The residue was purified by column chromatography on silica (10-50% EtOAc/P.E.) to afford the title compound.

Step 3: [4-[(4-methoxyphenyl)methoxy]-2-methylpyrimidin-5-yl]methanol

Into a 20-L 4-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed a solution of methyl 4-[(4-methoxyphenyl)methoxy]-2-methyl-

pyrimidine-5-carboxylate (600, 2.08 mol) in THF (7500 mL), followed by the addition of LAH (2.5M) (835 mL) dropwise with stirring at -10 °C. The resulting solution was stirred at -10°C for 1 h, and then quenched with EtOAc (2500 mL), and MeOH (2500 mL). The resulting mixture was concentrated under reduced pressure. The residue was purified by column chromatography on silica (1-10% MeOH/DCM) to afford the title compound. MS: 261 (M+1). ¹H NMR (300 MHz, CDCl₃): δ 8.332 (1H, s), 7.358-7.406 (2H, m), 6.888-6.936 (2H, m), 5.417 (2H, s), 4.615 (2H, s), 3.822 (2H, s), 2.641 (3H, s).

INTERMEDIATE C02



(2-chloro-4-methoxypyrimidin-5-yl)methanol

Step 1: 5-bromo-2-chloro-4-methoxypyrimidine

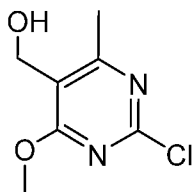
Into a 5000-mL 4-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 5-bromo-2,4-dichloropyrimidine (160 g, 702.14 mmol) and MeOH (3200 mL), followed by dropwise addition of MeONa (126.8 g, 1.00 equiv) with stirring at 0°C. The resulting solution was stirred at 0°C for 1 h, then concentrated under reduced pressure. The resulting solution was diluted with water (1 L). The solids were collected on top of a filter to afford the title compound.

Step 2: (2-chloro-4-methoxypyrimidin-5-yl)methanol

Into a 5000-mL 4-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 5-bromo-2-chloro-4-methoxypyrimidine (136 g, 608.62 mmol) and toluene (2500 mL), followed by dropwise addition of n-BuLi (256 mL, 1.05 equiv) with stirring at -78°C. After 30 min stirring at -78°C, HCOOCH₂CH₃ (90 g, 1.22 mol) was added to the reaction mixture dropwise. The resulting solution was stirred at -78 °C for another 30 min, and then MeOH (218 mL) was added dropwise, followed by addition of NaBH₄ (30 g, 793.02 mmol). The reaction solution was stirred at -78 °C for another 10 min before quenched by slow addition of water (1000 mL), and warmed up to 10 °C. The resulting mixture was extracted with EtOAc (2×2000 mL). The combined organic layers were washed with brine, dried over anhydrous

sodium sulfate, filtered and concentrated under reduced pressure. The residue was washed with PE (1000 mL), and collected on top of a filter to afford the title compound. MS: 175 (M+1). ¹H NMR (300MHz, CDCl₃, ppm): δ 8.36 (d, *J* = 0.9 Hz, 1H), 4.67 (d, *J* = 0.9 Hz, 2H), 4.08 (s, 3H).

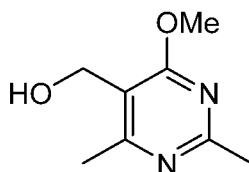
INTERMEDIATE C03



(2-chloro-4-methoxy-6-methylpyrimidin-5-yl)methanol

Intermediate C03 was prepared using a similar procedure outlined in the synthesis for intermediate C02 using 5-bromo-2-chloro-4-methoxy-6-methylpyrimidine. MS: 189 (M+1)

INTERMEDIATE C04



(4-methoxy-2,6-dimethylpyrimidin-5-yl)methanol

Step 1: 1,3-diethyl 2-(1-hydroxyethyl)propanedioate

Into a 50-L 4-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed a solution of 1,3-diethyl 2-acetylpropanedioate (5000 g, 24.73 mol) in AcOH (25 L). This was followed by the addition of NaBH₄ (1220 g, 32.25 mol) in several batches at 0°C over 1 h. The resulting solution was stirred at 0°C for 3h, and then quenched with water (2L), and extracted with DCM (3×5L). The combined organic layers were concentrated under reduced pressure. The residue was purified by column chromatography on silica (50% EtOAc/hexanes) to afford the title compound.

Step 2: 1,3-diethyl 2-[1-(acetyloxy)ethyl]propanedioate

Into a 50-L 4-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed a solution of 1,3-diethyl 2-(1-hydroxyethyl)propanedioate (3800 g, 18.61 mol) in DCM (38 L), acetic anhydride (2280 g, 22.35 mol), TEA (3762 g, 37.18 mol), 4-dimethylaminopyridine (454 g, 3.72 mol). The resulting solution was stirred at 60°C for 16 h,

then quenched by the addition of water (4 L), and extracted with DCM (3×5 L). The combined organic layers were concentrated under reduced pressure. The residue was purified by column chromatography on silica (2% EtOAc/P.E.) to afford the title compound.

Step 3: 1,3-diethyl 2-ethylidenepropanedioate

5 Into a 10-L 4-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed 1,3-diethyl 2-[1-(acetyloxy)ethyl]propanedioate (3200 g, 12.99 mol). This was followed by dropwise addition of acetaldehyde (1716 g, 38.95 mol) with stirring at 80°C over 40 min. The resulting solution was stirred at 80 °C for 16 h, then cooled to 20 °C and quenched by the addition of water (5 L), and then extracted with EtOAc (3×2 L). The combined
10 organic layers were concentrated under reduced pressure. The residue was purified by column chromatography on silica (0.5% EtOAc/P.E.) to afford the title compound.

Step 4: Ethyl 2,4-dimethyl-6-oxo-1,4,5,6-tetrahydropyrimidine-5-carboxylate

Into a 50-L 4-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed a solution of ethanimidamide hydrochloride (1060 g, 11.21 mol) in
15 ethanol (30 L), NaOEt (1380 g, 14.68 mol). This was followed by dropwise addition of a solution of 1,3-diethyl 2-ethylidenepropanedioate (1700 g, 9.13 mol) in ethanol (4 L) with stirring at 60°C over 30 min. The resulting solution was stirred at 60 °C for 2 h, and then cooled to 20 °C. The solid was filtered out. The filtrate was concentrated under reduced pressure to afford the title compound which was used as is in the next step.

20 Step 5: Ethyl 2,4-dimethyl-6-oxo-1,6-dihydropyrimidine-5-carboxylate

Into a 50-L 4-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed a solution of ethyl 2,4-dimethyl-6-oxo-1,4,5,6-tetrahydropyrimidine-5-carboxylate (2500 g, 12.61 mol) in 1,4-dioxane (25 L), potassium carbonate (7200 g, 52.09 mol), NBS (2300 g, 12.92 mol), BPO (78 g, 304.39 mmol). The resulting solution was stirred at 80°C
25 for 16 h. The reaction mixture was cooled to 20 °C, and then quenched by the addition of water (10 L). The pH value of the solution was adjusted to 7 with HCl. The resulting solution was extracted with DCM (3×5 L). The combined organic layers were concentrated under reduced pressure. The residue was purified by column chromatography on silica (5% MeOH/DCM) to afford the title compound.

30 Step 6: Ethyl 4-chloro-2,6-dimethylpyrimidine-5-carboxylate

Into a 50-L 4-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed ethyl 2,4-dimethyl-6-oxo-1,6-dihydropyrimidine-5-carboxylate (1100 g, 5.61 mol) and POCl₃ (11 L). The resulting solution was stirred at 80 °C for 5 h, then concentrated under reduced pressure to afford the title compound, which was used in the next step as is.

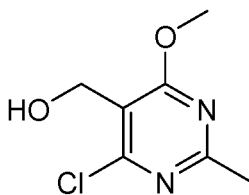
Step 7: Ethyl 4-methoxy-2,6-dimethylpyrimidine-5-carboxylate

Into a 50-L 4-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed a solution of ethyl 4-chloro-2,6-dimethylpyrimidine-5-carboxylate (2000 g, 9.32 mol) in MeOH (20 L). The resulting solution was stirred at RT for 2 h, and concentrated under reduced pressure. The residue was dissolved in water (5 L). The resulting solution was extracted with DCM (3×2 L). The combined organic layers were concentrated under reduced pressure. The residue was purified by column chromatography on silica (10% EtOAc/P.E.) to afford the title compound.

Step 8: (4-methoxy-2,6-dimethylpyrimidin-5-yl)methanol

Into a 10-L 4-necked round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed a solution of ethyl 4-methoxy-2,6-dimethylpyrimidine-5-carboxylate (270 g, 1.28 mol) in THF (2.7 L). This was followed by the addition of LAH (54 g, 1.42 mol) in several batches at 0°C over 30 min. The resulting solution was stirred at 0°C for 2 h, and then quenched by the addition of 15%NaOH (65 mL). After stirred for 1h, the solids were filtered out. The filtrate was concentrated under reduced pressure to afford the title compound. MS: 169 (M+1). ¹H NMR (400 MHz, CDCl₃): δ 4.678 (s, 2H), 3.988 (s, 3H), 2.562 (s, 3H), 2.493 (s, 3H).

INTERMEDIATE C05



(4-chloro-6-methoxy-2-methylpyrimidin-5-yl)methanol

Step 1: 4,6-dichloro-2-methylpyrimidine-5-carbaldehyde

To a solution of POCl₃ (31.4 mL, 337 mmol) was added DMF (2.90 g, 39.6 mmol) at 0°C, then the resulting mixture was stirred at 25°C for 0.5 h. Then 2-methylpyrimidine-4,6-diol (5 g,

39.6 mmol) was added. After being stirred at 25°C for 1 h, the reaction mixture was heated at 120°C for 10 h, and then poured onto ice (100 mL), and extracted with EtOAc (3×100 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtrated and concentrated under reduced pressure to afford the title compound which was used directly in the next step. MS: 190.9 (M+1).

Step 2: (4,6-dichloro-2-methylpyrimidin-5-yl)methanol

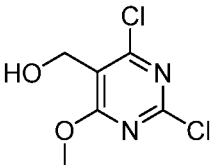
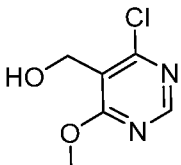
To a solution of 4,6-dichloro-2-methylpyrimidine-5-carbaldehyde (7.57 g, 39.6 mmol) in MeOH (75 mL) was added NaBH₄ (1.799 g, 47.6 mmol) at -40°C, then the mixture was stirred at 25°C. After 0.5 h, the reaction mixture was quenched with H₂O (100 mL), extracted with EtOAc (3×100 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtrated and concentrated under reduced pressure. The residue was purified by column chromatography on silica (5-33% EtOAc/P.E.) to afford the title compound. MS: 193.1 (M+1). ¹H NMR (400 MHz, CDCl₃): δ 4.91 (s, 2H), 2.69 (s, 3H).

Step 3: (4-chloro-6-methoxy-2-methylpyrimidin-5-yl)methanol

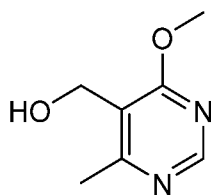
To a solution of (4, 6-dichloro-2-methylpyrimidin-5-yl) methanol (1 g, 5.18 mmol) in MeOH (10 mL) was added sodium methoxide (0.280 g, 5.18 mmol), then the mixture was stirred at 25°C for 4 h. The reaction mixture was then quenched with H₂O (10 mL), extracted with EtOAc (3×10 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtrated and concentrated under reduced pressure to obtain the title compound. MS: 189.1 (M+1).

The following intermediates in Table 4 were prepared using a similar procedure as outlined in the synthesis of intermediate C05, but replacing the 4,6-dichloro-2-methylpyrimidine-5-carbaldehyde in Step 2 with the appropriate chloro substituted pyrimidine-5-carbaldehyde.

TABLE 4

INT	Structure	IUPAC Name	MS (M+1)
C06		(2,4-dichloro-6-methoxypyrimidin-5-yl)methanol	211.4
C07		(4-chloro-6-methoxypyrimidin-5-yl)methanol	175.2

INTERMEDIATE C08

5 (4-methoxy-6-methylpyrimidin-5-yl)methanol

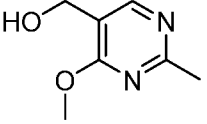
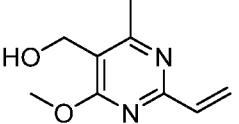
To a stirred solution of (4-chloro-6-methoxypyrimidin-5-yl)methanol (5 g, 28.6 mmol) in THF (100 mL) was added Cs₂CO₃ (18.66 g, 57.3 mmol) and trimethylboroxine (7.19 g, 57.3 mmol) in a sealed tube. After degassed with nitrogen for 5 min, 1,1'-bis(diphenyl phosphino)ferrocene-palladium(II)dichloride dichloromethane complex (2.339 g, 2.86 mmol) was added. The resulting mixture was heated at 70 °C for 7 h, and then filtered through CELITE[®], washed with EtOAc and concentrated under reduced pressure. The residue was purified with column chromatography on silica (50-80% EtOAc/P.E.) to afford the title compound. MS: 155.2 (M+1). ¹H NMR (300 MHz, CDCl₃): δ 8.332 (1H, s), 7.358-7.406 (2H, m), 6.888-6.936 (2H, m), 5.417 (2H, s), 4.615 (2H, s), 3.822 (2H, s), 2.641 (3H, s).

15

The following intermediates in Table 5 were prepared using a similar procedure as outlined in the synthesis of intermediate C08 but replacing the (4-chloro-6-methoxypyrimidin-5-

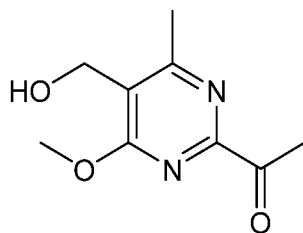
yl)methanol with (2-chloro-4-methoxypyrimidin-5-yl)methanol and methylboronic acid or vinylboronic acid.

TABLE 5

INT	Structure	IUPAC Name	MS (M+1)
C09		(4-methoxy-2-methylpyrimidin-5-yl)methanol	155.0
C10		(4-methoxy-6-methyl-2-vinylpyrimidin-5-yl)methanol	181.3

5

INTERMEDIATE C11



1-(5-(hydroxymethyl)-4-methoxy-6-methylpyrimidin-2-yl)ethan-1-one

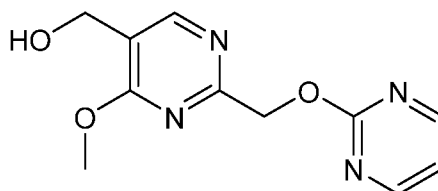
Step 1: (2-(1-ethoxyvinyl)-4-methoxy-6-methylpyrimidin-5-yl)methanol

To a stirred solution of (2-chloro-4-methoxy-6-methylpyrimidin-5-yl)methanol (80 mg, 0.424 mmol) in DMF (1 mL) was added Pd(Ph₃P)₄ (49.0 mg, 0.042 mmol) under N₂ and the resulting mixture was stirred at 100 °C for 2 h. Then the mixture was diluted in water (10 mL) extracted with EtOAc (3×20 mL). The combined organic layers were treated with sat. KF aq. (20 mL) and stirred at 20°C for 30 min before filtering over CELITE[®]. The filtrate was washed with water, brine, and dried over anhydrous Na₂SO₄, filtrated and concentrated under reduced pressure. The residue was purified by Preparative TLC plate(50% EtOAc/P.E.) to afford the title compound. ¹H NMR (400 MHz, CDCl₃): δ 4.71 (br s, 2 H), 4.58 (d, *J*=1.47 Hz, 1 H), 3.94 - 4.11 (m, 5 H), 2.59 (s, 3 H), 1.49 (t, *J*=7.03 Hz, 3 H).

Step 2: 1-(5-(hydroxymethyl)-4-methoxy-6-methylpyrimidin-2-yl)ethan-1-one

To a solution of (2-(1-ethoxyvinyl)-4-methoxy-6-methylpyrimidin-5-yl)methanol (130 mg, 0.580 mmol) in EtOAc (10 mL) was added 4N solution of HCl in EtOAc (5 mL). The resulting reaction mixture was stirred at 20 °C for 1 h, and then concentrated under reduced pressure to afford the title compound which was used into next step without purification. ¹H NMR (400 MHz, DMSO-*d*₆): δ 4.52 (s, 2 H), 3.99 (s, 3 H), 2.62 (s, 3 H), 2.55 (s, 3 H).

INTERMEDIATE C12



(4-methoxy-6-methyl-2-((pyrimidin-2-yloxy)methyl)pyrimidin-5-yl)methanol

Step 1: 5-(((tert-butyl)diphenylsilyl)oxy)methyl)-2-chloro-4-methoxy-6-methylpyrimidine

To a solution of (2-chloro-4-methoxy-6-methylpyrimidin-5-yl)methanol (0.8 g, 4.24 mmol) in THF (14 mL) was added 1*H*-imidazole (0.866 g, 12.72 mmol) and tertbutylchloro-diphenylsilane (1.749 g, 6.36 mmol). The resulting mixture was stirred at 20 °C for 2 h, and then quenched with water and extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica (1.25% EtOAc/P.E.) to afford the title compound. MS: 472.2 (M+1). ¹H NMR (400 MHz, CDCl₃) δ 1.03 (s, 9 H) 2.54 (s, 3 H) 3.80 (s, 3 H) 4.70 (s, 2 H) 7.34 - 7.49 (m, 6 H) 7.66 (dd, *J*=7.95, 1.34 Hz, 4 H).

Step 2: 5-(((tert-butyl)diphenylsilyl)oxy)methyl)-4-methoxy-6-methyl-2-vinylpyrimidine

To a solution of 5-(((tert-butyl)diphenylsilyl)oxy)methyl)-2-chloro-4-methoxy-6-methylpyrimidine (1.4 g, 3.28 mmol) in 1,4-dioxane (20 mL) and water (4 mL) was added K₂CO₃ (0.906 g, 6.56 mmol) and 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (1.010 g, 6.56 mmol) and PdCl₂(dppf) (0.240 g, 0.328 mmol). The resulting mixture was stirred at 100 °C for 2 h, and then diluted with water and extracted with EtOAc (3×30 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica (2% EtOAc/P.E.) to afford the title compound. MS: 419.3 (M+1). ¹H NMR (400 MHz, CDCl₃) δ

1.04 (s, 9 H) 2.56 (s, 3 H) 3.83 (s, 3 H) 4.74 (s, 2 H) 5.67 (dd, $J=10.30$, 1.97 Hz, 1 H) 6.51 - 6.62 (m, 1 H) 6.71 - 6.82 (m, 1 H) 7.34 - 7.48 (m, 6 H) 7.69 (dd, $J=7.89$, 1.32 Hz, 4 H).

Step 3: 5-(((tert-butyldiphenylsilyl)oxy)methyl)-4-methoxy-6-methylpyrimidine-2-carbaldehyde

To a solution of 5-(((tert-butyldiphenylsilyl)oxy)methyl)-4-methoxy-6-methyl-2-vinylpyrimidine (1.2 g, 2.87 mmol) in 1,4-Dioxane (30 mL) and water (10 mL) was added osmium(VIII) oxide (0.018 g, 0.072 mmol) and 2,6-dimethylpyridine (0.860 g, 8.03 mmol). The resulting mixture was stirred at 20 °C for 30 min before sodium periodate (2.269 g, 10.61 mmol) was added. The reaction mixture was stirred at 20 °C for 10 h, and then quenched with saturated aqueous solution of Na₂SO₃ (10 mL) and extracted with EtOAc (3×20 mL). The combined organic layers were washed with 1M HCl, brine, and dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford the title compound, which was used for the next step without further purification. MS: 421.3 (M+1). ¹H NMR (400 MHz, CDCl₃) δ 1.03 (s, 9 H) 2.68 (s, 2 H) 3.86 - 3.93 (m, 2 H) 4.79 (s, 2 H) 7.34 - 7.49 (m, 6 H) 7.61 - 7.70 (m, 4 H) 9.95 (s, 1 H).

Step 4: (5-(((tert-butyldiphenylsilyl)oxy)methyl)-4-methoxy-6-methylpyrimidin-2-yl)methanol

To a solution of 5-(((tert-butyldiphenylsilyl)oxy)methyl)-4-methoxy-6-methylpyrimidine-2-carbaldehyde (0.65 g, 1.545 mmol) in EtOH (40 mL) was added Zn(BH₄)₂ (0.386 mL, 0.386 mmol) at -10-0°C. The resulting solution was stirred at this temperature for 30 min before quenched with 4N HCl (5 mL), diluted with water (50 mL) and extracted with EtOAc (3×50 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford the title compound. MS: 423.3 (M+1). ¹H NMR (400 MHz, CDCl₃) δ 0.99 - 1.11 (m, 13 H) 2.59 (s, 3 H) 3.81 (s, 3 H) 4.68 (s, 2 H) 4.74 (s, 2 H) 7.33 - 7.49 (m, 8 H) 7.63 - 7.70 (m, 5 H).

Step 5: 5-(((tert-butyldiphenylsilyl)oxy)methyl)-4-methoxy-6-methyl-2-((pyrimidin-2-yloxy)methyl)pyrimidine

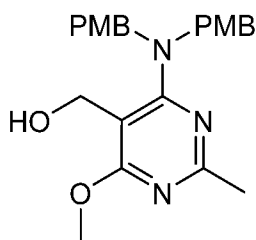
To a solution of (5-(((tert-butyldiphenylsilyl)oxy)methyl)-4-methoxy-6-methylpyrimidin-2-yl)methanol (90 mg, 0.213 mmol) in *t*-BuOH (5 mL) was added 2-chloropyrimidine (24.39 mg, 0.213 mmol) and *t*-BuOK (59.7 mg, 0.532 mmol) at 50 °C. The resulting reaction mixture was stirred at 50 °C for 2 h before diluted with water (20 mL) and extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and

concentrated under reduced pressure to afford the title compound, which was used to next step without purification. MS: 501.3 (M+1).

Step 6: (4-methoxy-6-methyl-2-((pyrimidin-2-yloxy)methyl)pyrimidin-5-yl)methanol

To a solution of 5-(((tert-butyldiphenylsilyl)oxy)methyl)-4-methoxy-6-methyl-2-
 5 ((pyrimidin-2-yloxy)methyl)pyrimidine (130 mg, 0.260 mmol) in THF (3 mL) was added TBAF
 (82 mg, 0.260 mmol) at 20°C. The resulting reaction mixture was stirred at 20 °C for 2 hrs
 before being diluted with water (50 mL) and extracted with EtOAc (3×50 mL). The combined
 organic extracts were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated
 under reduced pressure. The residue was purified by preparative TLC plate (100% EtOAc) to
 10 afford the title compound. MS: 263.1 (M+1).

INTERMEDIATE C13



(4-(Bis(4-methoxybenzyl)amino)-6-methoxy-2-methylpyrimidin-5-yl)methanol

Step 1: 4-(Bis(4-methoxybenzyl)amino)-6-chloro-2-methylpyrimidine-5-carbaldehyde

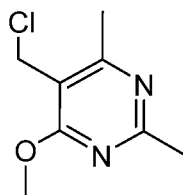
15 4,6-dichloro-2-methylpyrimidine-5-carbaldehyde (600 mg, 3.14 mmol) was dissolved in
 DCM (15.7 mL) and chilled to 0 °C where Hunig's base (1207 µL, 6.91 mmol) was added
 followed by the addition of bis(4-methoxybenzyl)amine (889 mg, 3.46 mmol). The solution was
 stirred at 0 °C for 4 h. The reaction was added to DCM (20 mL). The solution was washed with
 water (2×10 mL) and concentrated under reduced pressure. The residue was purified by column
 20 chromatography on silica (0-50% EtOAc/hexanes) to afford title compound. MS: 412.2 (M+1).

Step 2: (4-(Bis(4-methoxybenzyl)amino)-6-methoxy-2-methylpyrimidin-5-yl)methanol

4-(Bis(4-methoxybenzyl)amino)-6-chloro-2-methylpyrimidine-5-carbaldehyde (1.2 g,
 2.91 mmol) was added to a flask and was dissolved in THF (14.57 mL) and chilled to -78 °C
 where sodium methoxide (25% by weight in MeOH) (1.382 mL, 5.83 mmol) was added and
 25 stirred at 0 °C for 50 min. NaBH₄ (0.110 g, 2.91 mmol) was added at 0 °C and stirred for an
 additional 1 h. Water (1000 µL) was added to the solution at 0 °C and stirred for 10 min. Then

the solution was taken into DCM (20 mL) and washed with water (2×10 mL) and the organic was concentrated under reduced pressure to isolate the title compound. MS: 410.3 (M+1).

INTERMEDIATE C14



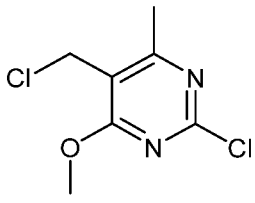
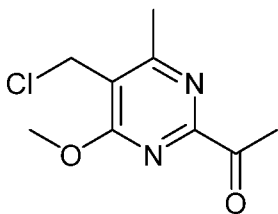
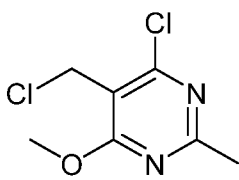
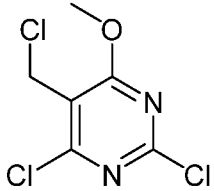
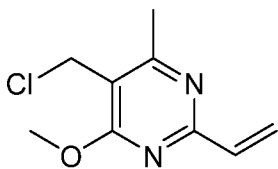
5-(chloromethyl)-4-methoxy-2,6-dimethylpyrimidine

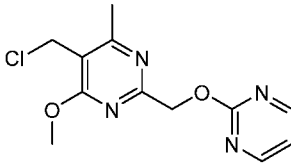
To a stirred solution of (4-methoxy-2,6-dimethylpyrimidin-5-yl)methanol, **C04** (1 g, 5.95 mmol) in DCM (15 mL) was added DIPEA (3.12 mL, 17.84 mmol) and MsCl (1.390 mL, 17.84 mmol) at 0°C under N₂. The resulting reaction mixture was stirred at 15°C for 2 h before diluted with water (15mL) and extracted with DCM (3×20mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica (1-33% EtOAc/P.E.) to afford the title compound. MS: 187 (M+1). ¹H NMR (400 MHz, CDCl₃): δ4.63 (s, 1 H) 4.01 (s, 1 H) 2.58 (s, 1 H) 2.52 (s, 1 H).

The following intermediates in Table 6 were prepared using a similar procedure as outlined in the synthesis of intermediate **C14** but replacing the (4-methoxy-2,6-dimethylpyrimidin-5-yl)methanol with a corresponding pyrimidin-5-ylmethanol that is listed as starting material in Table 6.

TABLE 6

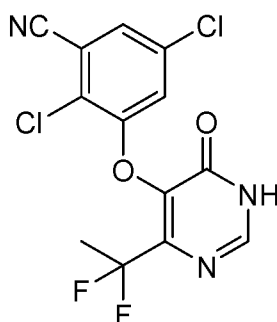
NT	Starting material	Structure	IUPAC Name	MS (M+1)
C15	C09		5-(chloromethyl)-4-methoxy-2-methylpyrimidine	173.0
C16	C08		5-(chloromethyl)-4-methoxy-6-methylpyrimidine	173.2

C20	C03		2-chloro-5-(chloromethyl)-4-methoxy-6-methylpyrimidine	207.0
C21	C11		1-(5-(chloromethyl)-4-methoxy-6-methylpyrimidin-2-yl)ethanone	215.1
C22	C05		4-chloro-5-(chloromethyl)-6-methoxy-2-methylpyrimidine	207.0
C23	C06		2,4-dichloro-5-(chloromethyl)-6-methoxypyrimidine	226.9
C24	C10		5-(chloromethyl)-4-methoxy-6-methyl-2-vinylpyrimidine	199.0

C25	C12		5-(chloromethyl)-4-methoxy-6-methyl-2-((pyrimidin-2-yl)oxy)methylpyrimidine	281.1
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Intermediate AB Section

INTERMEDIATE AB01



5 2,5-dichloro-3-((4-(1,1-difluoroethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile

Step 1: 3-bromo-5-((4-(1,1-difluoroethyl)-1-(4-methoxybenzyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile

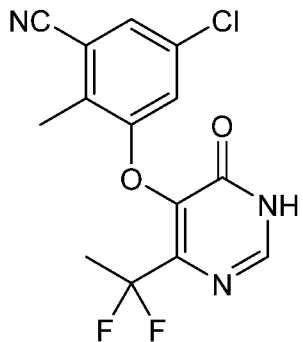
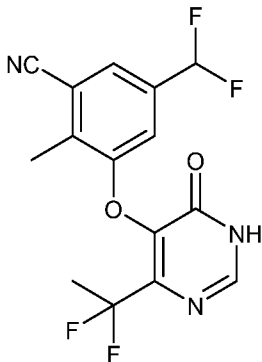
To a solution of 5-bromo-6-(1,1-difluoroethyl)-3-(4-methoxybenzyl)pyrimidin-4(3H)-one (MK8507 case) (100mg, 0.28 mmol) in NMP (0.5 mL) was added 2,5-dichloro-3-hydroxybenzonitrile, **A04** (105 mg, 0.56 mmol) and K₂CO₃ (192 mg, 1.39 mmol). The resulting reaction mixture was stirred at 140 °C for 2 h, and then filtered and purified by reverse phase HPLC (ACN/water with 0.1% TFA modifier) to afford the title compound as the TFA salt. MS: 477 (M+1).

Step 2: 2,5-dichloro-3-((4-(1,1-difluoroethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile

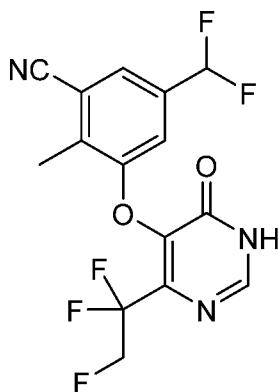
15 To a mixture of 2, 5-dichloro- 3 -((4-(1,1-difluoroethyl)-1-(4-methoxybenzyl)-6-oxo-1, 6-dihydropyrimidin-5-yl) oxy) benzonitrile (50 mg, 0.107 mmol) in TFA (2 mL), was add TFAA (0.227 mL, 1.609 mmol). The resulting solution was heated to 110 °C for 2 h, and then concentrated under the reduced pressure to afford the crude title compound, which was used directly in the next step without further purification. MS: 346.1 (M+1).

The following intermediates in Table 7 were prepared in an analogous manner as for the synthesis of intermediate **AB01** described above and summarized as follows: S_NAr reaction between 5-bromo-6-(1,1-difluoroethyl)-3-(4-methoxybenzyl)pyrimidin-4(3H)-one and
 5 a corresponding phenol from the **intermediate A** section, followed by deprotection to remove PMB group using TFA/TFAA.

TABLE 7

INT	Structure	IUPAC Name	MS (M+1)
AB02		5-chloro-3-((4-(1,1-difluoroethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile	326
AB03		3-((4-(1,1-difluoroethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-5-(difluoromethyl)-2-methylbenzonitrile	342

INTERMEDIATE AB04



5-(difluoromethyl)-2-methyl-3-((6-oxo-4-(1,1,2-trifluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile

Step 1: 5-(difluoromethyl)-3-((1-(4-methoxybenzyl)-6-oxo-4-(1,1,2-trifluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile

To a mixture of 5-fluoro-3-(4-methoxybenzyl)-6-(1,1,2-trifluoroethyl)pyrimidin-4(3H)-one, **B13** (0.075 g, 0.237 mmol) and K₂CO₃ (0.066 g, 0.474 mmol) in DMA (2 mL) was added 5-(difluoromethyl)-3-hydroxy-2-methylbenzonitrile, **A02** (0.043 g, 0.237 mmol) in one portion at 15 °C under N₂. The mixture was stirred at 100 °C for 16 h. The mixture was concentrated and diluted with EtOAc (5 mL), washed with H₂O and brine, dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by preparative TLC plates (100% EtOAc) to afford the title compound. MS: 480.2 (M+1).

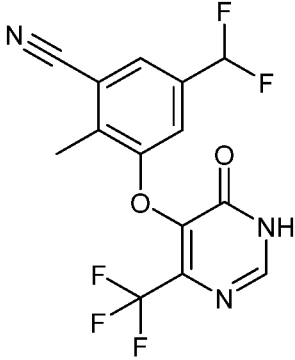
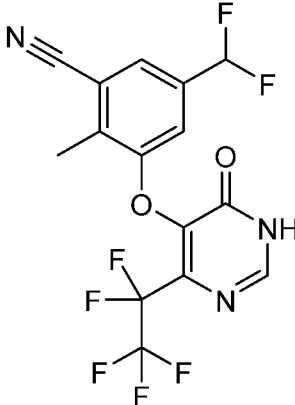
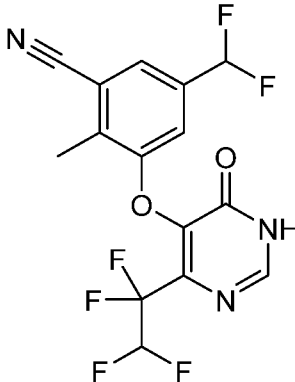
Step 2: 5-(difluoromethyl)-2-methyl-3-((6-oxo-4-(1,1,2-trifluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile

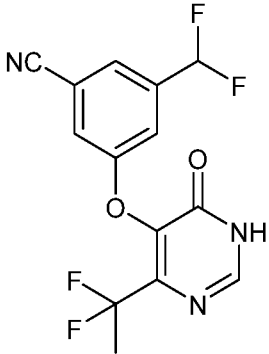
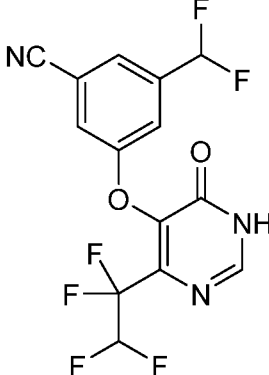
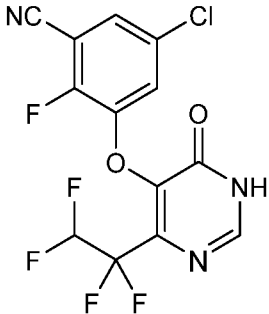
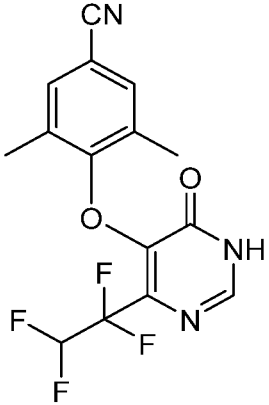
To a solution of 5-(difluoromethyl)-3-((1-(4-methoxybenzyl)-6-oxo-4-(1,1,2-trifluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile (70 mg, 0.146 mmol) in TFA (1 mL), was added TFAA (1 mL) and the mixture was stirred at 100 °C for 4 h. The mixture was concentrated and diluted with EtOAc (5 mL), washed with H₂O, saturated aqueous solution of NaHCO₃ and brine, dried over anhydrous Na₂SO₄, filtered and concentrated to give the crude title compound. MS: 360.1 (M+1).

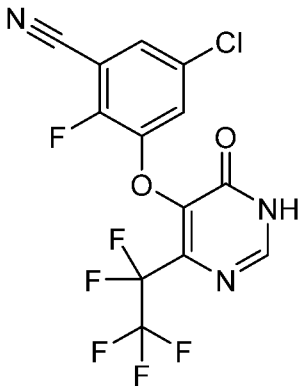
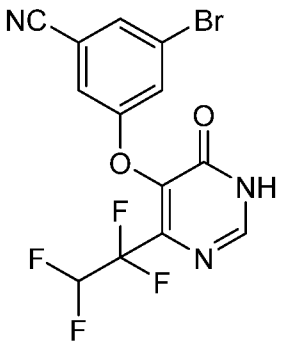
The following intermediates in Table 8 were prepared in an analogous manner as for the synthesis of intermediate **AB04** described above and summarized as follows: S_NAr

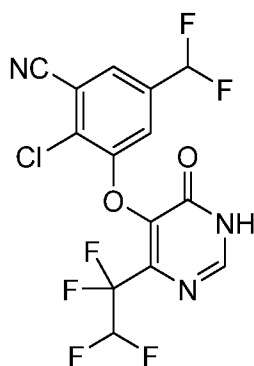
reaction using a phenol from **intermediate A** section and a pyrimidone from **intermediate B** section, then deprotection to remove PMB group using TFA/TFAA.

TABLE 8

INTER-MEDIA TE	Structure	IUPAC Name	MS (M+1)
AB05		5-(difluoromethyl)-2-methyl-3-((6-oxo-4-(trifluoromethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile	346.1
AB06		5-(difluoromethyl)-2-methyl-3-((6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile	396.1
AB07		5-(difluoromethyl)-2-methyl-3-((6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile	378.1

AB08		3-((4-(1,1-difluoroethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-5-(difluoromethyl)benzonitrile	328
AB09		3-(difluoromethyl)-5-((6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile	364.0
AB10		5-chloro-2-fluoro-3-((6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile	366.1
AB11		3,5-dimethyl-4-((6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile	341.9

AB12		5-chloro-2-fluoro-3-((6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile	384.0
AB13		3-bromo-5-((6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile	392.0

INTERMEDIATE AB14

2-chloro-5-(difluoromethyl)-3-((6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile

5

Step 1: 5-bromo-2-chloro-3-((1-(4-methoxybenzyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile

To a stirred solution of 5-fluoro-3-(4-methoxybenzyl)-6-(1,1,2,2-tetrafluoroethyl)-pyrimidin-4(3H)-one, **B15** (2g, 5.98 mmol), 5-bromo-2-chloro-3-hydroxybenzonitrile, **A03** (1.391 g, 5.98 mmol) in sulfolane (75 mL) was added K₂CO₃ (1.654 g, 11.97 mmol) and the mixture solution was stirred at 130 °C for 16 h. The mixture was diluted with water (4×50 mL) and extracted with EtOAc (3×50 mL). The combined organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica (25-100% EtOAc/P.E.) to afford the title compound. MS: 548.0 (M+1).

Step 2: 2-chloro-3-((1-(4-methoxybenzyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-5-vinylbenzonitrile

To a stirred solution of 5-bromo-2-chloro-3-((1-(4-methoxybenzyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile (1.45 g, 2.65 mmol) in 1,4-dioxane (24.07 mL) and water (4.93 mL), was added potassium vinyltrifluoroborate (0.426 g, 3.18 mmol), K₂CO₃ (0.733 g, 5.30 mmol) and PdCl₂(dppf) (0.194 g, 0.265 mmol) under N₂. The resulting mixture was heated to 100 °C for 2 h, and then diluted with water (50 mL) and extracted with EtOAc (3×30 mL). The combined organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica (25-100% EtOAc/P.E.) to give the title compound. MS: 494.1 (M+1).

Step 3: 2-chloro-5-formyl-3-((1-(4-methoxybenzyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile

To a solution of 2-chloro-3-((1-(4-methoxybenzyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-5-vinylbenzonitrile (950 mg, 1.924 mmol) in 1,4-dioxane (15 mL) and water (5 mL), was added osmium(VIII) oxide (98 mg, 0.385 mmol), 2,6-dimethylpyridine (206 mg, 1.924 mmol). The resulting mixture was stirred for 15 min before sodium periodate (1234 mg, 5.77 mmol) was added. The resulting mixture was stirred at 25 °C for 12 h, and then was quenched with saturate aqueous Na₂SO₃, diluted with water (50 mL) and extracted with EtOAc (3×30 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give the title compound. MS: 496.1 (M+1).

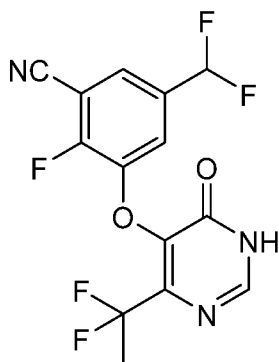
Step 4: 2-chloro-5-(difluoromethyl)-3-((1-(4-methoxybenzyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile

To a stirred solution of 2-chloro-5-formyl-3-((1-(4-methoxybenzyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile (950 mg, 1.916 mmol) in DCM (20 mL) was added DAST (2532 μ L, 19.16 mmol) and the mixture solution was stirred at 0 °C for 12 h. The mixture was diluted with water (40 mL) and extracted with DCM (3 $\times$ 30 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica (25-100% EtOAc/P.E.) to give the title compound. MS: 518.1 (M+1).

Step 5: 2-chloro-5-(difluoromethyl)-3-((6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile

A solution of 2-chloro-5-(difluoromethyl)-3-((1-(4-methoxybenzyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile (80 mg, 0.154 mmol) in TFA (1 mL) and TFAA (0.5 mL) was stirred at 110 °C for 1 h. The mixture was concentrated under reduced pressure. The residue was taken up with saturated aqueous NaHCO₃ (0.5 mL) and water (30 mL), and extracted with EtOAc (3 $\times$ 15 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford the title compound. MS: 398.0 (M+1).

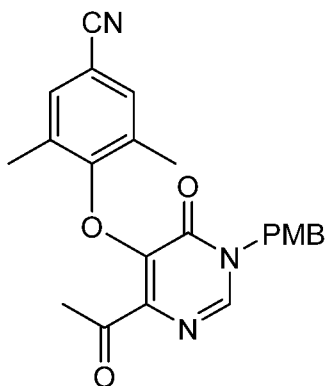
INTERMEDIATE AB15



3-((4-(1,1-difluoroethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-5-(difluoromethyl)-2-fluorobenzonitrile

Intermediate **AB15** was prepared in an analogous manner as that described for intermediate **AB14** using a corresponding intermediate A and intermediate B. MS: 346.1 (M+1).

INTERMEDIATE AB16

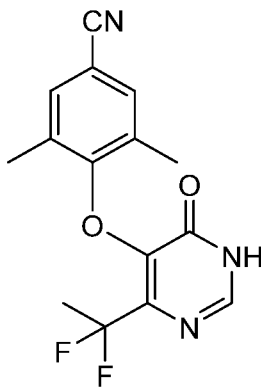


5 4-((4-acetyl-1-(4-methoxybenzyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-3,5-dimethylbenzonitrile

To a solution of 6-acetyl-5-fluoro-3-(4-methoxybenzyl) pyrimidin-4(3H)-one, **B11** (150 mg, 0.489 mmol) in DMA (1.000 mL) was added 4-hydroxy-3, 5-dimethylbenzonitrile (144 mg, 0.977 mmol) and K₂CO₃ (135 mg, 0.977 mmol). The resulting reaction mixture was stirred at
 10 80 °C for 40 min, and then diluted with water (5 mL), extracted with EtOAc (3×10 mL). The combined organic layers were washed with water, brine, filtrated and concentrated under reduced pressure. The residue was purified by preparative TLC plate (50% EtOAc/P.E.) to give the title compound. ¹H NMR (400 MHz, CDCl₃) δ 7.88 (s, 1H), 7.24 (s, 2H), 7.15 (s, 1H), 7.13 (s, 1H), 6.80 (d, *J*=8.8, 2H), 5.23 (s, 2H), 3.73 (s, 2H), 2.51 (s, 3H), 2.11 (s, 6H).

15

INTERMEDIATE AB17



3-chloro-4-((4-(1,1-difluoroethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-5-methylbenzonitrile
Step 1: 4-((4-(1,1-difluoroethyl)-1-(4-methoxybenzyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-
3,5-dimethylbenzonitrile

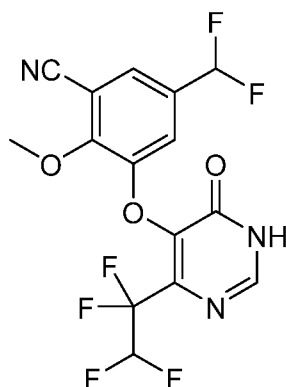
To a solution of 4-((4-acetyl-1-(4-methoxybenzyl)-6-oxo-1, 6-dihydropyrimidin-5-yl)
 5 oxy)-3, 5-dimethylbenzonitrile (160mg, 0.357 mmol) in DCM (3.0 mL) was added DAST
 (0.472 mL, 3.57 mmol) at 20 °C. The resulting reaction mixture was stirred at 50 °C for 18 h,
 and then diluted with water (3.0 mL), and extracted with DCM (3×5 mL). The combined
 organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtrated and concentrated
 under reduced pressure. The residue was purified by preparative TLC plate (50% EtOAc/P.E.)
 10 to afford the title compound. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.61 (s, 1H), 7.52 (s, 2H), 7.24
 (d, *J*=8.4, 2H), 6.89 (d, *J*=8.4, 2H), 4.99 (s, 2H), 3.72 (s, 3H), 2.06 (s, 6H), 1.99 (m, 3H).

Step 3: 4-((4-(1,1-difluoroethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-3,5-dimethylbenzonitrile

A suspension of 4-((4-(1,1-difluoroethyl)- 1 -(4-methoxybenzyl)- 6 -oxo-1,6-
 dihydropyrimidin-5-yl)oxy)-3, 5-dimethylbenzonitrile (100 mg, 0.212 mmol) in TFA (0.8mL,
 15 10.38 mmol) and TFAA (0.4 mL, 2.83 mmol) was stirred at 110 °C for 4 h. The reaction
 mixture was concentrated under reduced pressure. The residue was taken up with saturated
 aqueous NaHCO₃ adjusting pH to 9, and then extracted with DCM (3×10 mL). The combined
 organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtrated and concentrated
 under reduced pressure to give the title compound. MS: 306.1 (M+1).

20

INTERMEDIATE AB18



5-(difluoromethyl)-2-methoxy-3-((6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-
yl)oxy)benzonitrile

Step 1: 5-(3-bromo-5-(difluoromethyl)-2-methoxyphenoxy)-3-(4-methoxybenzyl)-6-(1,1,2,2-tetrafluoroethyl)pyrimidin-4(3H)-one

To a solution of 5-fluoro-3-(4-methoxybenzyl)-6-(1,1,2,2-tetrafluoroethyl)pyrimidin-4(3H)-one, **B15** (300 mg, 0.898 mmol) in DMF (5 mL) was added 3-bromo-5-(difluoromethyl)-2-methoxyphenol, **A08** (227 mg, 0.898 mmol) and K₂CO₃ (372 mg, 2.69 mmol). The reaction mixture was stirred at 80 °C for 2 h, and poured into H₂O (30 mL), extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine, filtered and concentrated under reduced pressure. The residue was purified by preparative TLC plate (33% EtOAc/P.E.) to afford the title compound. MS: 567.0 (M+1). ¹H NMR (400MHz, CDCl₃): δ 8.10 (s, 1H), 7.45 (s, 1H), 7.25 - 7.27 (m, 2H), 6.88 - 6.92 (m, 2H), 6.79 (s, 1H), 6.14 - 6.65 (m, 2H), 5.06 (s, 2H), 3.95 (s, 3H), 3.80 - 3.83 (m, 3H).

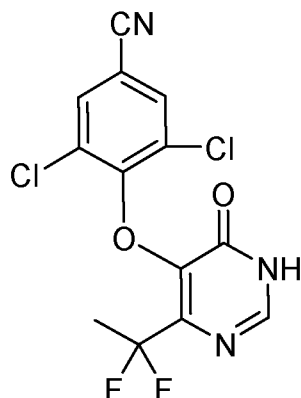
Step 2: 5-(difluoromethyl)-2-methoxy-3-((1-(4-methoxybenzyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile

To a solution of 5-(3-bromo-5-(difluoromethyl)-2-methoxyphenoxy)-3-(4-methoxybenzyl)-6-(1,1,2,2-tetrafluoroethyl)pyrimidin-4(3H)-one (140 mg, 0.247 mmol) in DMF (2 mL) was added dicyanozinc (145 mg, 1.234 mmol), zinc (32.3 mg, 0.494 mmol) and bis(tri-tert-butylphosphine)palladium(0) (25.2 mg, 0.049 mmol) under N₂. The resulting mixture was stirred at 110 °C for 12 h, and then filtered. The filtrate was diluted with H₂O (10 mL), extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give the title compound. MS: 514.0 (M+1).

Step 3: 5-(difluoromethyl)-2-methoxy-3-((6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile

To a solution of 5-(difluoromethyl)-2-methoxy-3-((1-(4-methoxybenzyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile (80 mg, 0.156 mmol) in TFA (1 mL) was added trifluoroacetic anhydride (0.440 mL, 3.12 mmol). The resulting reaction mixture was stirred at 110 °C for 1 h, and then concentrated under reduced pressure. The residue was purified by preparative TLC plate (33% EtOAc/P.E.) to give the title compound. MS: 394.1 (M+1).

INTERMEDIATE AB19



3,5-dichloro-4-((4-(1,1-difluoroethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile

Step1: 5-(4-bromo-2,6-dichlorophenoxy)-6-(1,1-difluoroethyl)-3-(4-methoxybenzyl)pyrimidin-4(3H)-one

A mixture of 5-bromo-6-(1,1-difluoroethyl)-3-(4-methoxybenzyl)pyrimidin-4(3H)-one (MK8507 case) (400 mg, 1.114 mmol) and 4-bromo-2,6-dichlorophenol (808 mg, 3.34 mmol) and K₂CO₃ (770 mg, 5.57 mmol) in NMP (10 mL) was stirred at 140°C for 27 h, and then diluted with H₂O (50 mL) and extracted with EtOAc (2×50 mL). The combined organic layers were washed brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by preparative TLC plate (50% EtOAc/P.E.) to afford the title compound.

MS: 521 (M+1).

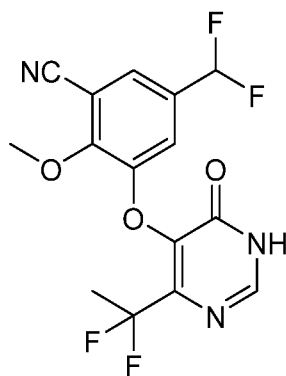
Step2: 3,5-dichloro-4-((4-(1,1-difluoroethyl)-1-(4-methoxybenzyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile

A mixture of 5-(4-bromo-2,6-dichlorophenoxy)-6-(1,1-difluoroethyl)-3-(4-methoxybenzyl)pyrimidin-4(3H)-one (200 mg, 0.385 mmol) and cyanocopper (172 mg, 1.923 mmol) in NMP (10 mL) was stirred at 180°C for 5 h. The reaction mixture was diluted with H₂O (40 mL) and extracted with EtOAc (2×30 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by preparative TLC plate (33% EtOAc/P.E.) to afford the title compound. MS: 647 (M+1).

Step 3: 3,5-dichloro-4-((4-(1,1-difluoroethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile

A solution of 3,5-dichloro-4-((4-(1,1-difluoroethyl)-1-(4-methoxybenzyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile (100 mg, 0.214 mmol) in TFA (2 mL, 0.214 mmol) and 2,2,2-trifluoroacetic anhydride (1 mL, 0.214 mmol) was stirred at 100°C for 4 h, and then concentrated under reduced pressure. The residue was taken up with saturated aqueous NaHCO₃ solution resulting in a solution with pH=7-8, and then extracted with EtOAc (2×20mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give the title compound, which was used for the next step without further purification. MS: 346 (M+1).

INTERMEDIATE AB20



3-((4-(1,1-difluoroethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-5-(difluoromethyl)-2-methoxybenzonitrile

Step 1: 6-acetyl-5-(3-bromo-5-(difluoromethyl)-2-methoxyphenoxy)-3-(4-methoxybenzyl)pyrimidin-4(3H)-one

A solution of 6-acetyl-5-fluoro-3-(4-methoxybenzyl)pyrimidin-4(3H)-one, **B11** (546 mg, 1.976 mmol), K₂CO₃ (819 mg, 5.93 mmol) and 3-bromo-5-(difluoromethyl)-2-methoxyphenol, **A08** (500 mg, 1.976 mmol) in DMF (10 mL) was stirred at 80 °C for 2 h, and then poured into water (50 mL), and extracted with EtOAc (3×30 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica (5-20% EtOAc/P.E.) to give the title compound. MS: 509.0 (M+1).

Step 2: 5-(3-bromo-5-(difluoromethyl)-2-methoxyphenoxy)-6-(1,1-difluoroethyl)-3-(4-methoxybenzyl)pyrimidin-4(3H)-one

To a solution of 6-acetyl-5-(3-bromo-5-(difluoromethyl)-2-methoxyphenoxy)-3-(4-methoxybenzyl)pyrimidin-4(3H)-one (470 mg, 0.923 mmol) in DCM (10 mL) was added DAST (1.219 mL, 9.23 mmol). The resulting reaction mixture was stirred at 20 °C for 1 h, and then poured into saturated aqueous NaHCO₃ (50 mL) dropwise, extracted with DCM (3×30 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica (3.3- 25% EtOAc/P.E.) to afford the title compound. MS: 531.0 (M+1).

Step 3: 3-((4-(1,1-difluoroethyl)-1-(4-methoxybenzyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-5-(difluoromethyl)-2-methoxybenzonitrile

To a solution of 5-(3-bromo-5-(difluoromethyl)-2-methoxyphenoxy)-6-(1,1-difluoroethyl)-3-(4-methoxybenzyl)pyrimidin-4(3H)-one (335.6 mg, 0.632 mmol) in DMF (5 mL) was added dicyanozinc (371 mg, 3.16 mmol), zinc (83 mg, 1.263 mmol) and Pd(tBu₃P)₂ (97 mg, 0.189 mmol) under N₂. The resulting mixture was stirred at 110 °C for 12 h, and then diluted with H₂O (25 mL), and extracted with EtOAc (3×15 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give the title compound. MS: 478.4 (M+1).

Step 4: 3-((4-(1,1-difluoroethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-5-(difluoromethyl)-2-methoxybenzonitrile

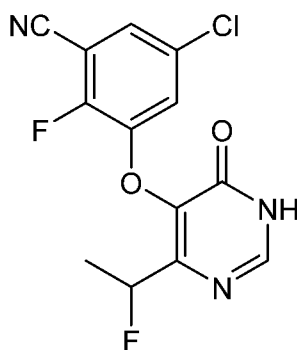
To a solution of 3-((4-(1,1-difluoroethyl)-1-(4-methoxybenzyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-5-(difluoromethyl)-2-methoxybenzonitrile (141 mg, 0.295 mmol) in TFA (2 mL) was added TFAA (1 mL, 7.08 mmol). The resulting reaction mixture was stirred at 110 °C for 0.5 h, then carefully poured into ice water (5 mL), extracted with EtOAc (3×3 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by preparative TLC plate (50% EtOAc/P.E.) to afford the title compound. MS: 358.0 (M+1).

The following intermediates in Table 9 were prepared in an analogous manner as for the synthesis of **intermediate AB20** using a corresponding phenol from **Intermediate A** section.

TABLE 9

INT	Structure	IUPAC Name	MS (M+1)
AB21		3-chloro-4-(((4-(1,1-difluoroethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-5-methylbenzonitrile	325.7
AB22		4-(((4-(1,1-difluoroethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-3-methyl-5-(trifluoromethyl)benzonitrile	360.1
AB23		3-(((4-(1,1-difluoroethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-2,4,5-trifluorobenzonitrile	332.1

INTERMEDIATE AB24



5-chloro-2-fluoro-3-((4-(1-fluoroethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile

Step 1: 6-acetyl-5-(3-bromo-5-chloro-2-fluorophenoxy)-3-(4-methoxybenzyl)pyrimidin-4(3H)-one

To a solution of 6-acetyl-5-fluoro-3-(4-methoxybenzyl)pyrimidin-4(3H)-one, **B11** (2 g, 7.24 mmol) in DMF (10 mL) was added 3-bromo-5-chloro-2-fluorophenol, **A05** (1.959 g, 8.69 mmol) and K_2CO_3 (2.001 g, 14.48 mmol). The resulting mixture was stirred at 60 °C for 4 h, and then poured into H_2O (100 mL), extracted with EtOAc (3×50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica (2-3.3% MeOH/DCM) to give the title compound.

Step 2: 5-(3-bromo-5-chloro-2-fluorophenoxy)-6-(1-hydroxyethyl)-3-(4-methoxybenzyl)pyrimidin-4(3H)-one

To a solution of 6-acetyl-5-(3-bromo-5-chloro-2-fluorophenoxy)-3-(4-methoxybenzyl)pyrimidin-4(3H)-one (300 mg, 0.623 mmol) in THF (2 mL) was added 0.1 M solution of $Zn(BH_4)_2$ in THF (0.934 mL, 0.093 mmol) at -30°C and the mixture was stirred for 10 min. The reaction mixture was added water (1 drop) and then concentrated under reduced pressure to afford the title compound.

Step 3: 5-(3-bromo-5-chloro-2-fluorophenoxy)-6-(1-fluoroethyl)-3-(4-methoxybenzyl)pyrimidin-4(3H)-one

To a solution of 5-(3-bromo-5-chloro-2-fluorophenoxy)-6-(1-hydroxyethyl)-3-(4-methoxybenzyl)pyrimidin-4(3H)-one (680 mg, 1.406 mmol) in DCM (10 mL) was added DAST (0.427 mL, 3.23 mmol) at 0 °C. The resulting reaction mixture was stirred at 0 °C for 1 h, and

then diluted with water (5 mL), extracted with DCM (3×10 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtrated and concentrated under reduced pressure to give the title compound.

Step 4: 5-chloro-2-fluoro-3-((4-(1-fluoroethyl)-1-(4-methoxybenzyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile

To a stirred solution of 5-(3-bromo-5-chloro-2-fluorophenoxy)-6-(1-fluoroethyl)-3-(4-methoxybenzyl)pyrimidin-4(3H)-one (340 mg, 0.700 mmol) in NMP (3 mL) was added cyanocopper (217 mg, 2.423 mmol) under N₂. The resulting mixture was stirred at 170 °C for 12 h, and then diluted with H₂O (30 mL) and EtOAc (30 mL). The mixture was filtered through CELITE[®]. The filtrate was extracted with EA (3×30 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was triturated with MeOH (20 mL) to afford the title compound.

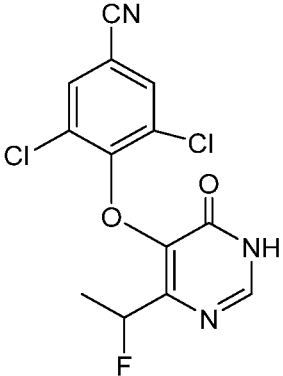
Step 5: 5-chloro-2-fluoro-3-((4-(1-fluoroethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile

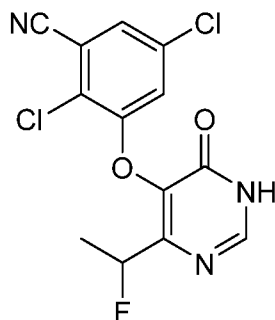
To a solution of 5-chloro-2-fluoro-3-((4-(1-fluoroethyl)-1-(4-methoxybenzyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile (0.217 g, 0.503 mmol) in TFA (1.5 mL) was added TFAA (0.75 mL). The resulting mixture was stirred at 100 °C for 6 h, and then diluted with DCM (10 mL), and concentrated under reduced pressure to afford the title compound.

The following intermediate in Table 10 was prepared in an analogous manner to that described above for intermediate **AB24** except using 4-bromo-2,6-dichlorophenol in place of 3-bromo-5-chloro-2-fluorophenol in Step 1.

TABLE 10

INT	Structure	IUPAC Name	MS (M+1)
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AB25		3,5-dichloro-4-((4-(1-fluoroethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile	328.0
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INTERMEDIATE AB26

2,5-dichloro-3-((4-(1-fluoroethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile

5 Step 1: 3-((4-acetyl-1-(4-methoxybenzyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-2,5-dichlorobenzonitrile

To a solution of 6-acetyl-5-fluoro-3-(4-methoxybenzyl)pyrimidin-4(3H)-one, **B11** (1.5 g, 5.43 mmol) in sulfolane (15 mL) was added 2,5-dichloro-3-hydroxybenzonitrile, **A04** (1.531 g, 8.14 mmol) and K₂CO₃ (1.876 g, 13.57 mmol). The resulting mixture was stirred at 60 °C for 2
10 h, and then diluted with water (60 mL) and extracted with EtOAc (3×45 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica (50-

15 tetrahydropyrimidin-5-yl)oxy)benzonitrile

To a solution of 3-((4-acetyl-1-(4-methoxybenzyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-2,5-dichlorobenzonitrile (800 mg, 1.801 mmol) in THF (10 mL), was added NaBH₄ (68.1 mg, 1.801 mmol). The resulting mixture was stirred at 25 °C for 0.5 h, and then quenched with water (30 mL), extracted with EtOAc (3×25 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica (33% EtOAc/P.E.) to afford the title compound. MS: 448.1 (M+1).

Step 3: 2,5-dichloro-3-((4-(1-hydroxyethyl)-1-(4-methoxybenzyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile

To a solution of 2,5-dichloro-3-((6-(1-hydroxyethyl)-3-(4-methoxybenzyl)-4-oxo-1,2,3,4-tetrahydropyrimidin-5-yl)oxy)benzonitrile (300 mg, 0.669 mmol) in H₂O (1 mL) and ACN (4 mL), was added CAN (734 mg, 1.338 mmol). The resulting mixture was stirred at 25 °C for 0.5 h, and then quenched with water (16 mL), extracted with EtOAc (3×12 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford the title compound. MS: 446.1 (M+1).

Step 4: 2,5-dichloro-3-((4-(1-fluoroethyl)-1-(4-methoxybenzyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile

To a solution of 2,5-dichloro-3-((4-(1-hydroxyethyl)-1-(4-methoxybenzyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile (173.3 mg, 0.388 mmol) in DCM (4 mL) was added DAST (0.513 mL, 3.88 mmol). The resulting mixture was stirred at 25 °C for 1 h, and then carefully quenched with saturated aqueous NaHCO₃ (16 mL), extracted with DCM (3×12 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica (20% EtOAc/P.E.) to afford the title compound. MS: 448.3 [M]⁺.

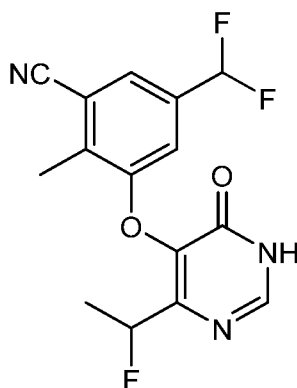
Step 5: 2,5-dichloro-3-((4-(1-fluoroethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile

To a solution of 2,5-dichloro-3-((4-(1-fluoroethyl)-1-(4-methoxybenzyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile (380 mg, 0.848 mmol) in TFA (5 mL) was added TFAA (5 mL, 35.4 mmol). The resulting mixture was stirred at 100 °C for 0.5 h, and then carefully quenched with saturated aqueous NaHCO₃ solution (20 mL), extracted with EtOAc (3×15 mL).

The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and

concentrated under reduced pressure to afford the title compound, which was used for the next step without further purification. MS: 382.2 [M]⁺.

INTERMEDIATE AB27



5

5-(difluoromethyl)-3-((4-(1-fluoroethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile

Step 1: 3-((4-acetyl-1-(4-methoxybenzyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-5-(difluoromethyl)-2-methylbenzonitrile

10

To a solution of 5-(difluoromethyl)-3-hydroxy-2-methylbenzonitrile, **A02** (0.663 g, 3.62 mmol) and 6-acetyl-5-fluoro-3-(4-methoxybenzyl)pyrimidin-4(3H)-one, **B11** (1.0g, 3.62 mmol) in DMF (10 mL) was added K₂CO₃ (1.001 g, 7.24 mmol). The resulting mixture was stirred at 60 °C for 2 h, and then diluted with water (30 mL), extracted with EtOAc (3×20 mL).

15 The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give the title compound. MS: 440.2 (M+1).

Step 2: 5-(difluoromethyl)-3-((6-(1-hydroxyethyl)-3-(4-methoxybenzyl)-4-oxo-1,2,3,4-tetrahydropyrimidin-5-yl)oxy)-2-methylbenzonitrile

20 To a solution of 3-((4-acetyl-1-(4-methoxybenzyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-5-(difluoromethyl)-2-methylbenzonitrile (1.5 g, 3.41 mmol) in MeOH (8 mL), was added NaBH₄ (0.129 g, 3.41 mmol). The resulting mixture was stirred at 25 °C for 0.5 h, and then quenched with water (30 mL), extracted with EtOAc (3×25 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford the title compound. MS: 444.1 (M+1).

Step 3: 5-(difluoromethyl)-3-((4-(1-hydroxyethyl)-1-(4-methoxybenzyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile

To a stirred solution of 5-(difluoromethyl)-3-((6-(1-hydroxyethyl)-3-(4-methoxybenzyl)-4-oxo-1,2,3,4-tetrahydropyrimidin-5-yl)oxy)-2-methylbenzonitrile (1g, 2.255 mmol) in THF (12 mL) was added DDQ (0.563 g, 2.481 mmol). The resulting mixture was stirred at 25 °C for 12 h, and then diluted with water (30 mL), extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica (50-100% EtOAc/P.E.) to afford the title compound. MS: 442.1 (M+1).

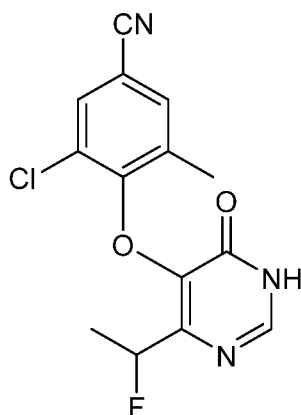
Step 4: 5-(difluoromethyl)-3-((4-(1-fluoroethyl)-1-(4-methoxybenzyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile

To a stirred solution of 5-(difluoromethyl)-3-((4-(1-hydroxyethyl)-1-(4-methoxybenzyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile (900 mg, 1.631 mmol) in DCM (8 mL) was added DAST (2.155 mL, 16.31 mmol). The resulting mixture was stirred at 0 °C for 4 h, and then diluted with water (20 mL), extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica (50-100% EtOAc/P.E.) to afford the title compound. MS: 444.2 (M+1).

Step 5: 5-(difluoromethyl)-3-((4-(1-fluoroethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile

A solution of 5-(difluoromethyl)-3-((4-(1-fluoroethyl)-1-(4-methoxybenzyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile (300 mg, 0.677 mmol) in TFA (2 mL) and TFAA (1 mL) was stirred at 110 °C for 0.5 h, and then concentrated under reduced pressure. Then mixture was diluted with EtOAc (2 mL) and quenched with saturated aqueous NaHCO₃ solution (5 mL). The aqueous layer was further extracted with EtOAc (20 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford the title compound. MS: 324.1 (M+1).

INTERMEDIATE AB28



3-chloro-4-((4-(1-fluoroethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-5-methylbenzonitrile

Step 1: 6-acetyl-5-(4-bromo-2-chloro-6-methylphenoxy)-3-(4-methoxybenzyl)pyrimidin-4(3H)-one

To a solution of 6-acetyl-5-fluoro-3-(4-methoxybenzyl)pyrimidin-4(3H)-one, **B11** (1.1 g, 3.98 mmol) in DMF (15 mL) was added 4-bromo-2-chloro-6-methylphenol (1.058 g, 4.78 mmol) and potassium carbonate (1.101 g, 7.96 mmol). The resulting mixture was stirred at 60 °C for 2 h, and then concentrated under reduced pressure. The residue was diluted with water (10 mL), and extracted with EtOAc (3×20 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica (0-50% EtOAc/P.E.) to afford the title compound. MS: 478.8 (M+1).

Step 2: 5-(4-bromo-2-chloro-6-methylphenoxy)-6-(1-hydroxyethyl)-3-(4-methoxybenzyl)-2,3-dihydropyrimidin-4(1H)-one

To a solution of 6-acetyl-5-(4-bromo-2-chloro-6-methylphenoxy)-3-(4-methoxybenzyl)pyrimidin-4(3H)-one (1.2 g, 2.51 mmol) in EtOAc (6 mL) and THF (9 mL), added 0.1 M solution of Zn(BH₄)₂ in THF (0.50 mL, 0.05 mmol) at -30 °C. The resulting mixture was stirred at -30 °C for 5 min, and then diluted by water (50 mL), extracted with EtOAc (3×50 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford the title compound. MS: 483.0 (M+1).

Step 3: 5-(4-bromo-2-chloro-6-methylphenoxy)-6-(1-hydroxyethyl)-3-(4-methoxybenzyl)pyrimidin-4(3H)-one

To a solution of 5-(4-bromo-2-chloro-6-methylphenoxy)-6-(1-hydroxyethyl)-3-(4-methoxybenzyl)-2,3-dihydropyrimidin-4(1H)-one (1 g, 2.08 mmol) in THF (10 mL) was added 4,5-dichloro-3,6-dioxocyclohexa-1,4-diene-1,2-dicarbonitrile (0.236 g, 1.04 mmol). The resulting reaction mixture was stirred at 25 °C for 0.5 h, and then diluted with water (50 mL),
 5 extracted with EA (3×50 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica (0-50% EtOAc/P.E.) to afford the title compound. MS: 481.0 (M+1).

Step 4: 5-(4-bromo-2-chloro-6-methylphenoxy)-6-(1-fluoroethyl)-3-(4-methoxybenzyl)pyrimidin-4(3H)-one

10 To a solution of 5-(4-bromo-2-chloro-6-methylphenoxy)-6-(1-hydroxyethyl)-3-(4-methoxybenzyl)pyrimidin-4(3H)-one (550 mg, 1.15 mmol) in DCM (11 mL) was added DAST (0.757 mL, 5.73 mmol) at 0 °C. The resulting reaction mixture was stirred at 0 °C for 1 h, and then carefully quenched with water (15 mL), and extracted with DCM (3×20 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtrated and concentrated
 15 under reduced pressure. The residue was purified by column chromatography on silica (0-20% EtOAc/P.E.) to afford the title compound. MS: 483.0 (M+1). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.51 - 1.66 (m, 3H) 2.18 (s, 3H) 3.72 (s, 3H) 4.92 - 5.04 (m, 2H) 5.89 - 6.16 (m, 1H) 6.89 (d, *J*=8.82 Hz, 2H) 7.23 (br d, *J*=7.28 Hz, 2H) 7.46 (br d, *J*=18.74 Hz, 2H) 8.57 (s, 1H).

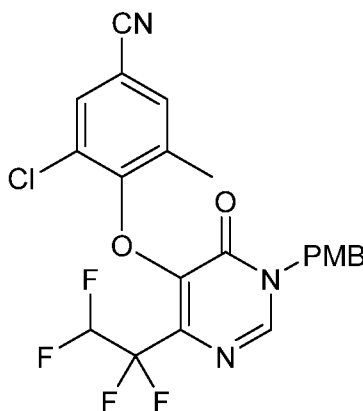
Step 5: 3-chloro-4-((4-(1-fluoroethyl)-1-(4-methoxybenzyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-5-methylbenzonitrile

20 To a stirred solution of 5-(4-bromo-2-chloro-6-methylphenoxy)-6-(1-fluoroethyl)-3-(4-methoxybenzyl)pyrimidin-4(3H)-one (383 mg, 0.80 mmol) in NMP (6 mL) was added cyanocopper (712 mg, 7.95 mmol) under N₂. The resulting mixture was stirred at 180 °C for 7 h, and then cooled to 25°C, diluted with H₂O (20 mL) and EtOAc (20 mL), then filtered over
 25 CELITE[®]. The filtrate was extracted with EA (3×20 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford the title compound. MS: 428.0 (M+1).

Step 6: 3-chloro-4-((4-(1-fluoroethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-5-methylbenzonitrile

A mixture of 3-chloro-4-((4-(1-fluoroethyl)-1-(4-methoxybenzyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-5-methylbenzonitrile (600mg, 1.40mmol) in TFA (10 mL) and TFAA (5mL) was heated at 100 °C for 16 h. The resulting mixture was concentrated under reduced pressure to afford the title compound, which was used in following steps directly without further purification. MS: 308.1 (M+1).

INTERMEDIATE AB29



3-cyclopropyl-5-methyl-4-((6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile

Step 1: 5-(4-bromo-2-chloro-6-methylphenoxy)-3-(4-methoxybenzyl)-6-(1,1,2,2-tetrafluoroethyl)pyrimidin-4(3H)-one

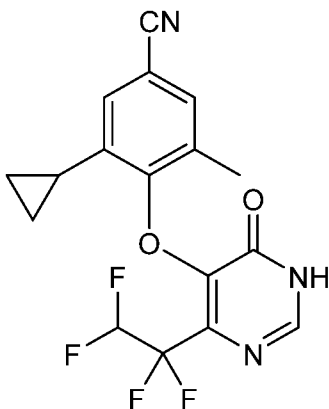
To a stirred solution of 5-fluoro- 3 -(4-methoxybenzyl)- 6 -(1,1,2,2-tetrafluoroethyl) pyrimidin-4(3H)-one, **B15** (700 mg, 2.094 mmol) in NMP (10 mL) was added 4-bromo-2-chloro-6-methylphenol (696 mg, 3.14 mmol) and potassium carbonate (868 mg, 6.28 mmol).

The resulting mixture was stirred at 120°C for 2 h, and then diluted with H₂O (15mL) and extracted with EtOAc (3×15mL). The combined organic layers were washed with H₂O and brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica (10-50% EtOAc/P.E.) to afford the title compound. ¹HNMR (400 MHz, CDCl₃): δ7.94 (s, 1H) 7.32 (d, *J*=2.08 Hz, 1H) 7.28 (d, *J*=2.08 Hz, 1H) 7.22 (d, *J*=8.56 Hz, 2H) 6.90 (d, *J*=8.68 Hz, 2H) 6.21 - 6.55 (m, 1H) 4.99 (d, *J*=2.45 Hz, 2H) 3.81 (s, 3H) 2.29 (s, 3H).

Step 2: 3-chloro-4-((1-(4-methoxybenzyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-5-methylbenzonitrile

To a stirred solution of 5-(4-bromo-2-chloro-6-methylphenoxy)-3-(4-methoxybenzyl)-6-(1,1,2,2-tetrafluoroethyl)pyrimidin-4(3H)-one (800 mg, 1.49 mmol) in DMF (25 mL) was added dicyanozinc (193 mg, 1.64 mmol) and Pd(Ph₃P)₄ (173 mg, 0.15 mmol) under N₂. The resulting mixture was stirred at 80°C for 2 h, and then diluted with EtOAc (25 mL). The mixture was washed with H₂O and brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica (10-50% EtOAc/P.E.) to afford the title compound. ¹H NMR (400 MHz, CDCl₃): δ 7.98 (s, 1H) 7.43 - 7.50 (m, 2H) 7.22 (d, *J*=8.68 Hz, 2H) 6.87 - 6.93 (m, 2H) 6.19 - 6.52 (m, 1H) 4.94 - 5.05 (m, 2H) 3.82 (s, 3H) 2.35 (s, 3H).

INTERMEDIATE AB30



3-cyclopropyl-5-methyl-4-((6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile

Step 1: 3-cyclopropyl-4-((1-(4-methoxybenzyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-5-methylbenzonitrile

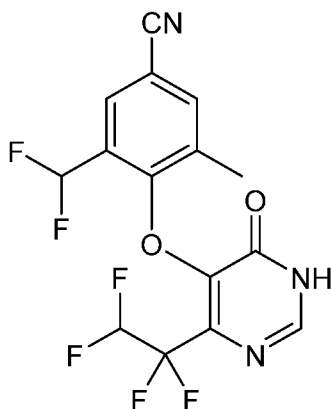
To a stirred solution of 3-chloro-4-((1-(4-methoxybenzyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-5-methylbenzonitrile, **AB29** (150 mg, 0.31 mmol), cyclopropylboronic acid (134 mg, 1.56 mmol), potassium phosphate tribasic (396 mg, 1.868 mmol) and di((3*S*,5*S*,7*S*)-adamantan-1-yl)(butyl)phosphine (67.0 mg, 0.19 mmol) in toluene (5 mL) and H₂O (1 mL), was added Pd(OAc)₂ (20.97 mg, 0.093 mmol) under N₂. The resulting mixture was stirred at 130°C for 16 h, and then passed through CELITE®. The filter cake was washed with DCM (10 mL) and MeOH (10 mL). The filtrate was concentrated under reduced pressure. The residue was purified by preparative TLC plate (33% EtOAc/P.E.) to

afford the title compound. ¹H NMR (400 MHz, CDCl₃): δ 7.89 (s, 1H) 7.27 (s, 1H) 7.14 (d, *J* = 8.56 Hz, 2H) 7.01 (s, 1H) 6.81 (d, *J* = 8.56 Hz, 2H) 6.14 - 6.48 (m, 1H) 4.78 - 5.00 (m, 2H) 3.74 (s, 3H) 2.17 (s, 3H) 1.65 - 1.73 (m, 1H) 0.64 - 0.79 (m, 2H) 0.39 - 0.51 (m, 1H) 0.20 (br dd, *J* = 9.90, 4.16 Hz, 1H).

5 Step 4: 3-cyclopropyl-5-methyl-4-((6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile

A solution of 3-cyclopropyl- 4 -((1-(4-methoxybenzyl)- 6 -oxo-4-(1,1,2,2-tetrafluoroethyl)-1, 6-dihydropyrimidin-5-yl)oxy)-5-methylbenzonitrile (130 mg, 0.27 mmol) in TFA (2 mL) and TFAA (1 mL) was stirred at 110°C for 3 h, and then cooled to RT, carefully
 10 quenched by adding saturated aqueous NaHCO₃ solution (10 mL), and extracted with EtOAc (3×5mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford the title compound. MS: 368.1 (M+1).
¹H NMR (400 MHz, CDCl₃): δ 8.80 (s, 1H) 7.78 - 7.83 (m, 1H) 7.33 (s, 1H) 7.11 (s, 1H) 6.28 - 6.57 (m, 1H) 2.26 (s, 3H) 1.80 - 1.86 (m, 1H) 0.86 - 0.92 (m, 1H) 0.68 - 0.84 (m, 2H) 0.39 - 0.52
 15 (m, 1H).

INTERMEDIATE AB31



3-(difluoromethyl)-5-methyl-4-((6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile

20 Step 1: 4-((1-(4-methoxybenzyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-3-methyl-5-vinylbenzonitrile

To a stirred solution of 3-chloro- 4 -((1-(4-methoxybenzyl)- 6 -oxo-4-(1,1,2,2-tetrafluoroethyl)-1, 6-dihydropyrimidin-5-yl)oxy)-5-methylbenzonitrile, **AB29** (370 mg, 0.77

mmol) in 1,4-dioxane (5 mL) and H₂O (1 mL) was added potassium trifluoro(vinyl)-borate (514 mg, 3.84 mmol), K₂CO₃ (637 mg, 4.61 mmol), dicyclohexyl(2',4',6'-triisopropyl-[1,1'-biphenyl]-2-yl)phosphine (146 mg, 0.307 mmol) and diacetoxypalladium (34.5 mg, 0.154 mmol) under N₂. The resulting mixture was stirred at 120°C for 18 h, and then filtered over CELITE[®]. The filter cake was washed with MeOH (10mL) and DCM (10mL). The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica (10-50% EtOAc/P.E.) to afford the title compound. ¹H NMR (400 MHz, CDCl₃): δ 7.95 (s, 1H) 7.54 (d, *J* = 2.08 Hz, 1H) 7.41 (d, *J* = 1.83 Hz, 1H) 7.16 - 7.19 (m, 2H) 6.86 - 6.89 (m, 2H) 6.69 (dd, *J* = 17.48, 11.00 Hz, 1H) 6.19 - 6.54 (m, 1H) 5.53 (d, *J* = 17.48 Hz, 1H) 5.17 - 5.28 (m, 1H) 4.81 - 5.04 (m, 2H) 3.81 (s, 3H) 2.24 (s, 3H).

Step 2: 3-formyl-4-((1-(4-methoxybenzyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-5-methylbenzonitrile

To a stirred solution of 4-((1-(4-methoxybenzyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-3-methyl-5-vinylbenzonitrile (100 mg, 0.21 mmol) in 1,4-dioxane (1 mL) and water (0.33 mL), was added 2,6-dimethylpyridine (45.3 mg, 0.42 mmol), sodium periodate (136 mg, 0.63 mmol) and osmium(VIII) oxide (2.69 mg, 10.56 μmol). The resulting mixture was stirred at 15 °C for 1 h, and then quenched with saturated aqueous Na₂SO₃ solution (15 mL) and extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by preparative TLC plates (50% EtOAc/P.E.) to afford the title compound. ¹H NMR (400 MHz, CDCl₃): δ 10.16 (s, 1H) 7.99 (s, 1H) 7.68 (s, 1H) 7.42 - 7.46 (m, 1H) 7.17 - 7.20 (m, 2H) 6.88 - 6.91 (m, 2H) 6.13 - 6.55 (m, 1H) 4.95 (d, *J* = 3.18 Hz, 2H) 3.81 (s, 3H) 2.25 (s, 3H).

Step 3: 3-(difluoromethyl)-4-((1-(4-methoxybenzyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-5-methylbenzonitrile

To a stirred solution of 3-formyl-4-((1-(4-methoxybenzyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-5-methylbenzonitrile (90 mg, 0.19 mmol) in DCM (1.5 mL) was added diethylaminosulfurtrifluoride (30.429 mg, 1.89 mmol) under N₂. The resulting mixture was stirred at 15 °C for 2 h, and then carefully poured into saturated aqueous solution of NaHCO₃ (20mL), extracted with DCM (3×20 mL). The combined organic layers

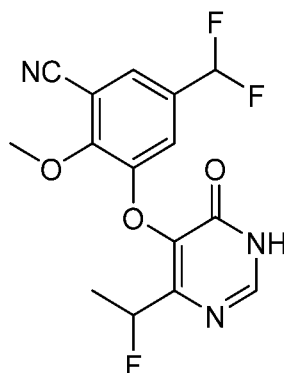
were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by preparative TLC plates (50% EtOAc/P.E.) to afford the title compound. MS: 498 (M+1).

Step 4: 3-(difluoromethyl)-5-methyl-4-((6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile

A solution of 3-(difluoromethyl)-4-((1-(4-methoxybenzyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-5-methylbenzonitrile (60 mg, 0.072 mmol) in TFA (2 mL) and TFAA (1 mL) was stirred at 110°C for 1 h. The mixture was quenched by adding saturated aqueous solution of NaHCO₃ (15mL) and extracted with EtOAc (3×10 mL).

The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to the title compound. MS: 378 (M+1).

INTERMEDIATE AB32



5-(difluoromethyl)-3-((4-(1-fluoroethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-2-methoxybenzonitrile

Step 1: 6-acetyl-5-(3-bromo-5-(difluoromethyl)-2-methoxyphenoxy)-3-(4-methoxybenzyl)pyrimidin-4(3H)-one

To a solution of 6-acetyl-5-fluoro-3-(4-methoxybenzyl)pyrimidin-4(3H)-one, **B11** (460 mg, 1.67 mmol) in DMF (5 mL) was added 3-bromo-5-(difluoromethyl)-2-methoxyphenol, **A08** (463 mg, 1.83 mmol) and K₂CO₃ (460 mg, 3.33 mmol). The resulting reaction mixture was stirred at 60 °C for 4 h, and then quenched with saturated NH₄Cl solution, extracted with EtOAc (3×25 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the title compound. MS: 511.1 (M+1).

Step 2: 6-acetyl-5-(3-bromo-5-(difluoromethyl)-2-methoxyphenoxy)-3-(4-methoxybenzyl)-2,3-dihydropyrimidin-4(1H)-one

To a solution of 6-acetyl-5-(3-bromo-5-(difluoromethyl)-2-methoxyphenoxy)-3-(4-methoxybenzyl)pyrimidin-4(3H)-one (650 mg, 1.28 mmol) in MeOH (3 mL) was added NaBH₄ (121 mg, 3.19 mmol) at 0 °C for 10 min, and then quenched with saturated aqueous NH₄Cl solution, extracted with EtOAc (3×25 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford the title compound. MS: 513.2 (M+1).

Step 3: 5-(3-bromo-5-(difluoromethyl)-2-methoxyphenoxy)-6-(1-hydroxyethyl)-3-(4-methoxybenzyl)pyrimidin-4(3H)-one

To a solution of 5-(3-bromo-5-(difluoromethyl)-2-methoxyphenoxy)-6-(1-hydroxyethyl)-3-(4-methoxybenzyl)-2,3-dihydropyrimidin-4(1H)-one (480 mg, 0.94 mmol) in THF (2 mL) was added DDQ (425 mg, 1.87 mmol) at 25 °C for 1 h, TLC (50% EtOAc/P.E.) showed the reaction was completed. The reaction mixture was diluted with H₂O (20 mL), extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give the title compound, which was used in following step directly without further purification. MS: 513.2 (M+1).

Step 4: 5-(3-bromo-5-(difluoromethyl)-2-methoxyphenoxy)-6-(1-fluoroethyl)-3-(4-methoxybenzyl)pyrimidin-4(3H)-one

To a solution of 5-(3-bromo-5-(difluoromethyl)-2-methoxyphenoxy)-6-(1-hydroxyethyl)-3-(4-methoxybenzyl)pyrimidin-4(3H)-one (280 mg, 0.55 mmol) in DCM (4 mL) was added DAST (0.739 mL, 5.59 mmol) at 25 °C. The resulting mixture was stirred at 25 °C for 1 h, and then carefully quenched with water (100 mL), extracted with EtOAc (3×100 mL). The combined organic layers were washed with water, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by column chromatography on silica (50% EtOAc/P.E.) to afford the title compound. MS: 513.2 (M+1).

Step 5: 5-(difluoromethyl)-3-((4-(1-fluoroethyl)-1-(4-methoxybenzyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-2-methoxybenzonitrile

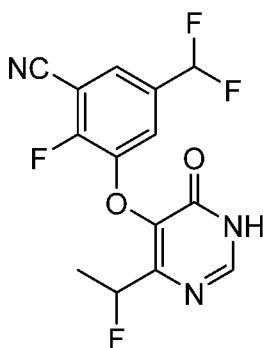
To a solution of 5-(3-bromo-5-(difluoromethyl)-2-methoxyphenoxy)-6-(1-fluoroethyl)-3-(4-methoxybenzyl)pyrimidin-4(3H)-one (60 mg, 0.12 mmol) in DMF (2 mL) was added

dicyanozinc (68.6 mg, 0.58 mmol), zinc (22.93 mg, 0.35 mmol) and bis(tri-tert-butylphosphine)palladium(0) (59.7 mg, 0.12 mmol) under N₂. The resulting mixture was stirred at 140 °C for 16 h. TLC (50% EtOAc/P.E.) showed the starting material was consumed. The mixture was diluted with water (40 mL) and extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by preparative TLC plates (50% EtOAc/P.E.) to afford the title compound. MS: 460.2 (M+1).

Step 6: 5-(difluoromethyl)-3-((4-(1-fluoroethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-2-methoxybenzonitrile

A solution of 5-(3-bromo-5-(difluoromethyl)-2-methoxyphenoxy)-3-(4-methoxybenzyl)-6-(1,1,2,2-tetrafluoroethyl)pyrimidin-4(3H)-one (50 mg, 0.088 mmol) in TFAA (0.5 mL, 3.54 mmol) and TFA (1 mL) was stirred at 110 °C for 2 h. TLC (50% EtOAc/P.E.) showed the reaction was completed. The reaction mixture was diluted with H₂O (10 mL), and extracted with EtOAc (3×10 mL). The combined organic was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford the title compound. MS: 340.2 (M+1).

INTERMEDIATE AB33



5-(difluoromethyl)-2-fluoro-3-((4-(1-fluoroethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile

Step 1: 6-acetyl-5-(3-bromo-5-chloro-2-fluorophenoxy)-3-(4-methoxybenzyl)pyrimidin-4(3H)-one

A solution of 6-acetyl-5-fluoro-3-(4-methoxybenzyl)pyrimidin-4(3H)-one, **B11** (3 g, 10.86 mmol), 3-bromo-5-chloro-2-fluorophenol, **A05** (3.37 g, 11.95 mmol), and K₂CO₃ (4.50 g, 32.6 mmol) in DMF (30 mL) was stirred at 50 °C for 1 h, and then diluted with water (50 mL) and extracted with EtOAc (3×50 mL). The combined organic layers were washed with brine,

dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica (0-50% EtOAc/P.E.) to afford the title compound. ¹H NMR (400 MHz, DMSO-d₆): δ 2.49 (s, 3H) 2.49 - 2.49 (m, 1H) 3.73 (s, 3H) 5.08 (s, 2H) 6.91 (d, *J*=8.68 Hz, 2H) 7.21 (dd, *J*=6.91, 2.38 Hz, 1H) 7.33 (br d, *J*=8.68 Hz, 2H) 7.54 (dd, *J*=5.14, 2.45 Hz, 1H) 8.78 (s, 1H)

Step 2: 5-(3-bromo-5-chloro-2-fluorophenoxy)-6-(1-hydroxyethyl)-3-(4-methoxybenzyl)-2,3-dihydropyrimidin-4(1H)-one

To a solution of 6-acetyl-5-(3-bromo-5-chloro-2-fluorophenoxy)-3-(4-methoxybenzyl)pyrimidin-4(3H)-one (3 g, 6.23 mmol) in MeOH (10 mL) and THF (20 mL), was added NaBH₄ (0.236 g, 6.23 mmol). The resulting mixture was stirred at 20 °C for 1 h. TLC (50% EtOAc/P.E.) and LC-MS show there was desired product. The reaction mixture was diluted with water (50 mL) and extracted with EtOAc (3×50 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give the title compound, which was used in following step directly without further purification.

MS: 487.1 (M+1).

Step 3: 5-(3-bromo-5-chloro-2-fluorophenoxy)-6-(1-hydroxyethyl)-3-(4-methoxybenzyl)pyrimidin-4(3H)-one

A mixture of 5-(3-bromo-5-chloro-2-fluorophenoxy)-6-(1-hydroxyethyl)-3-(4-methoxybenzyl)-2,3-dihydropyrimidin-4(1H)-one (2.7 g, 5.56 mmol), and CAN (6.09 g, 11.12 mmol) in ACN (20 mL) and water (5 mL) was stirred at 20 °C for 20 min. TLC (50% EtOAc/P.E.) showed there was the desired product. The reaction mixture was diluted with water (50 mL), and extracted with EtOAc (3×50 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica (0-50% EtOAc/P.E.) to afford the title compound. MS: 485.0 (M+1).

Step 4: 5-(3-bromo-5-chloro-2-fluorophenoxy)-6-(1-fluoroethyl)-3-(4-methoxybenzyl)pyrimidin-4(3H)-one

To a solution of 5-(3-bromo-5-chloro-2-fluorophenoxy)-6-(1-hydroxyethyl)-3-(4-methoxybenzyl)pyrimidin-4(3H)-one (1.7 g, 3.51 mmol), and DAST (4.64 mL, 35.1 mmol) in DCM (17 mL) was stirred at 20 °C for 1 h. TLC (100% EtOAc) showed there was desired

product. The reaction mixture was diluted with water (50 mL) and extracted with EtOAc (3×50 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica (0-20% EtOAc/P.E.) to afford the title compound. ¹H NMR (400 MHz, DMSO-*d*₆): δ 1.49 - 1.59 (m, 3H) 3.73 (s, 3H) 5.06 (d, *J*=2.87 Hz, 2H) 5.65 - 5.84 (m, 1H) 6.90 (d, *J*=8.60 Hz, 2H) 7.15 (dd, *J*=6.84, 2.21 Hz, 1H) 7.32 (d, *J*=8.60 Hz, 2H) 7.55 (dd, *J*=5.07, 2.43 Hz, 1H) 8.74 (s, 1H).

Step 5: 5-chloro-2-fluoro-3-((4-(1-fluoroethyl)-1-(4-methoxybenzyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile

To a solution of 5-(3-bromo-5-chloro-2-fluorophenoxy)-6-(1-fluoroethyl)-3-(4-methoxybenzyl)pyrimidin-4(3H)-one (1.4 g, 2.88 mmol), and cyanocopper (2.58 g, 28.8 mmol) in NMP (25 mL) was stirred at 180 °C for 3.5 h. TLC (50% EtOAc/P.E.) and LC-MS showed there was desired product. The reaction mixture was diluted with EtOAc (50 mL), and passed through a filter. The filter cake was washed with EtOAc (20 mL) and H₂O (50 mL). The filtrate was extracted with EtOAc (3×50 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica (0-50% EtOAc/P.E.) to afford the title compound. MS: 432.1 (M+1).

Step 6: 2-fluoro-3-((4-(1-fluoroethyl)-1-(4-methoxybenzyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-5-vinylbenzonitrile

To a stirred solution of 5-chloro-2-fluoro-3-((4-(1-fluoroethyl)-1-(4-methoxybenzyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile (200 mg, 0.46 mmol) in 1,4-dioxane (4 mL) and water (0.8 mL) was added potassium trifluoro(vinyl)borate (93 mg, 0.70 mmol), di((3*S*,5*S*,7*S*)-adamantan-1-yl)(butyl)phosphine (66.4 mg, 0.185 mmol), K₃PO₄ (197 mg, 0.926 mmol), diacetoxypalladium (20.80 mg, 0.093 mmol) was added under N₂. The resulting mixture was stirred at 110 °C for 2 h. TLC (50% EtOAc/P.E.) and LC-MS showed the completion of the reaction. The mixture was diluted with water (25 mL) and extracted with EtOAc (3×25 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by preparative TLC plates (1% MeOH/DCM) to afford the title compound. MS: 424.2 (M+1).

Step 7: 2-fluoro-3-((4-(1-fluoroethyl)-1-(4-methoxybenzyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-5-formylbenzonitrile

To a solution of 2-fluoro-3-((4-(1-fluoroethyl)-1-(4-methoxybenzyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-5-vinylbenzonitrile (300 mg, 0.71 mmol) in 1,4-dioxane (10 mL) and water (3 mL), was added osmium(VIII) oxide (4.50 mg, 0.018 mmol) and 2,6-dimethylpyridine (213 mg, 1.98 mmol). The resulting mixture was stirred at 20 °C for 0.5 h, then sodium periodate (561 mg, 2.62 mmol) was added. The mixture was stirred at 20 °C for another 3 h. TLC (50% EtOAc/P.E.) and LC-MS showed the complete conversion. The reaction was quenched with saturated aqueous Na₂SO₃ solution (10 mL) and extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by preparative TLC plates (2% MeOH/ DCM) to give the title compound. MS: 426.2 (M+1).

Step 8: 5-(difluoromethyl)-2-fluoro-3-((4-(1-fluoroethyl)-1-(4-methoxybenzyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile

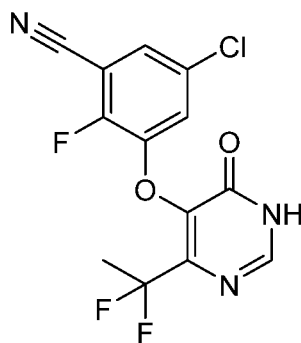
To a solution of 2-fluoro-3-((4-(1-fluoroethyl)-1-(4-methoxybenzyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-5-formylbenzonitrile (300 mg, 0.71 mmol) in DCM (0.5 mL) was added DAST (0.932 mL, 7.05 mmol). The resulting mixture was stirred at 20 °C for 2 h when TLC (50% EtOAc/P.E.) and LC-MS showed complete conversion. The reaction was quenched with saturated aqueous NaHCO₃ solution (10 mL) and extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by preparative TLC plates (50% EtOAc/P.E.) to afford the title compound. MS: 448.2 (M+1). ¹H NMR (400 MHz, DMSO-d₆): δ 1.51 - 1.62 (m, 3H) 3.73 (s, 3H) 4.98 - 5.15 (m, 2H) 5.67 - 5.93 (m, 1H) 6.80 - 7.12 (m, 3H) 7.31 (d, J=8.68 Hz, 2H) 7.57 (br d, J=6.48 Hz, 1H) 7.91 (br d, J=3.55 Hz, 1H) 8.79 (s, 1H).

Step 9: 5-(difluoromethyl)-2-fluoro-3-((4-(1-fluoroethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile-notebook page

To a solution of 5-(difluoromethyl)-2-fluoro-3-((4-(1-fluoroethyl)-1-(4-methoxybenzyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile (160 mg, 0.36 mmol) in TFA (7 mL) and TFAA (3.5 mL) was stirred at 100 °C for 3 h. TLC (50% EtOAc/P.E.) and LC-MS showed complete conversion. The reaction mixture was concentrated under reduced pressure to dryness.

The residual was diluted in EtOAc (2 mL), and then washed with saturated aqueous NaHCO₃ solution and brine, and concentrated under reduced pressure to afford the title compound, which was used in the next step directly without further purification. MS: 328.0 (M+1).

INTERMEDIATE AB34



5-Chloro-3-((4-(1,1-difluoroethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-2-fluorobenzonitrile

Step 1: Methyl 5-fluoro-1-(4-methoxybenzyl)-6-oxo-1,6-dihydropyrimidine-4-carboxylate

Potassium carbonate (16.11 g, 117 mmol) was added to a mixture of methyl 5-fluoro-1-(4-methoxybenzyl)-6-oxo-1,6-dihydropyrimidine-4-carboxylate, **B14** (21.29 g, 72.9 mmol) and 5-chloro-2-fluoro-3-hydroxybenzonitrile, **A06** (10 g, 58.3 mmol) in dimethylacetamide (350 mL) at 25 °C. The resulting mixture was stirred at 90 °C overnight. LC-MS showed desired product and clean reaction. Water (500 mL) was added and a precipitate was formed. The mixture was filtered and the solid was washed with water (100 mL) and hexanes (200 mL) and dried overnight under high vacuum to provide the title compound. MS: 444 (M+1).

Step 2: 5-(5-Chloro-3-cyano-2-fluorophenoxy)-1-(4-methoxybenzyl)-6-oxo-1,6-dihydropyrimidine-4-carboxylic acid

Potassium trimethylsilanolate (9.97 g, 78 mmol) was added to a stirring mixture of methyl 5-(5-chloro-3-cyano-2-fluorophenoxy)-1-(4-methoxybenzyl)-6-oxo-1,6-dihydropyrimidine-4-carboxylate (23 g, 51.8 mmol) in THF (345 mL). The resulting mixture was stirred at 25 °C for 1 h. LC-MS showed only desired product. HCl (1N aq., 300 mL) was added slowly and a white solid was formed. The mixture was concentrated under reduced pressure to remove THF. The mixture was filtered and the white solid was washed with water and dried under vacuum to provide the title compound. MS: 430.0 (M+1).

Step 3: 5-(5-Chloro-3-cyano-2-fluorophenoxy)-N-methoxy-1-(4-methoxybenzyl)-N-methyl-6-oxo-1,6-dihydropyrimidine-4-carboxamide

To a flask containing 5-(5-chloro-3-cyano-2-fluorophenoxy)-1-(4-methoxybenzyl)-6-oxo-1,6-dihydropyrimidine-4-carboxylic acid (20 g, 46.5 mmol) and *N,O*-dimethylhydroxylamine hydrochloride (4.99 g, 51.2 mmol) in DMF (200 mL), was added triethylamine (25.9 mL, 186 mmol) followed by EDC (9.81 g, 51.2 mmol) and HOBt (7.84 g, 51.2 mmol) at 25 °C. The resulting mixture was stirred at 25 °C overnight. LC-MS indicated the completion of the reaction. Water (300 mL) was added and the resulting precipitate was filtered and washed with water, dried under vacuum to provide the title compound. MS: 473.1 (M+1).

Step 4: 3-((4-Acetyl-1-(4-methoxybenzyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-5-chloro-2-fluorobenzonitrile

Methylmagnesium bromide (3M in THF, 40 mL, 120 mmol) was added dropwise to a cooled (-78 °C) mixture of 5-(5-chloro-3-cyano-2-fluorophenoxy)-*N*-methoxy-1-(4-methoxybenzyl)-*N*-methyl-6-oxo-1,6-dihydropyrimidine-4-carboxamide (16.5 g, 34.9 mmol) in THF (350 mL). The resulting mixture was stirred at -78°C for 3h. LC-MS showed desired product but still starting material. The reaction mixture was then warmed up to 0 °C and stirred for 30 min. LC-MS indicated completion of the reaction. The reaction was quenched with saturated aqueous NH₄Cl solution (500 mL) and diluted with EtOAc (200 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2×200 mL). The combined organic layers were washed with brine (500 mL), dried over anhydrous MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica (0-100% EtOAc/hexanes) to afford the title compound. MS: 428.0 (M+1).

Step 5: 5-Chloro-3-((4-(1,1-difluoroethyl)-1-(4-methoxybenzyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-2-fluorobenzonitrile

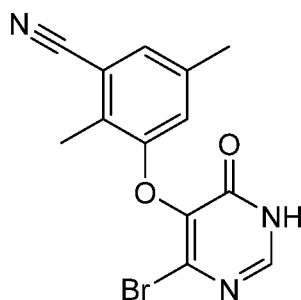
DEOXOFLUOR® (15.08 mL, 82 mmol) was added to vial containing 3-((4-acetyl-1-(4-methoxybenzyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-5-chloro-2-fluorobenzonitrile (7 g, 16.36 mmol) and dichloroethane (9.35 mL) at 25 °C. The resulting vial was sealed and stirred at 70 °C for 3 h. LC-MS showed desired product. The reaction was cooled to room temperature and poured into a saturated NaHCO₃ solution very slowly and carefully. Then, the organic layer was separated and the aqueous layer was extracted with dichloromethane (2 x 100 mL). The

combined organic layers were dried over MgSO₄, filtered and concentrated. The residue was purified by column chromatography on silica (0-100% EtOAc/hexanes) to afford the title compound. MS: 450.0 (M+1).

Step 6: 5-Chloro-3-((4-(1,1-difluoroethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-2-fluorobenzonitrile

A flask containing a mixture of 5-chloro-3-((4-(1,1-difluoroethyl)-1-(4-methoxybenzyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-2-fluorobenzonitrile (7 g, 15.56 mmol) in trifluoroacetic acid (58.4 mL) and trifluoroacetic anhydride (19.45 mL) was stirred at 80 °C for 4 h. After cooling to room temperature, the mixture was concentrated under reduced pressure. The residue was dissolved in dichloromethane (50 mL) and hexanes (100 mL) were added slowly until the formation of a white solid. After stirring for 30 min, the white solid was collected on top of a filter, and dried under vacuum to provide the title compound. MS: 330.0 (M+1).

INTERMEDIATE AB35



3-((4-bromo-1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-2,5-dimethylbenzonitrile

Step 1: Dimethyl 2-(5-chloro-3-cyano-2-methylphenoxy)malonate

To a solution of 5-chloro-3-hydroxy-2-methylbenzonitrile, **A07** (12 g, 71.6 mmol) was added potassium carbonate (19.79 g, 143 mmol). The resulting mixture was stirred for 15 minutes before dimethyl 2-chloromalonate (13.12 g, 79 mmol) was added. The reaction mixture was heated at 80°C for 16 h. After cooled to room temperature, reaction mixture was concentrated under reduced pressure, then diluted with water and extracted with EtOAc. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica (6% EtOAc/P.E.) to afford the title compound.

Step 2: 5-chloro-3-((4-hydroxy-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile

To a solution of formamidine acetate (9.09 g, 87 mmol) in MeOH (120 mL) was added sodium methoxide (9.44 g, 175 mmol) and the reaction mixture was stirred at RT for 5 minutes, and then was added dimethyl 2-(5-chloro-3-cyano-2-methylphenoxy)malonate (13g, 43.7 mmol) portion wise. The reaction mixture was heated at 80°C for 1 h. After cooled to room temperature, the reaction mixture was concentrated under reduced pressure to remove MeOH. The residue was dissolved in water (50 mL) and acidified to pH=5 by using 1.5M HCl. The precipitate was collected on top of a filter, washed with EtOAc to afford the crude title compound which was used as is in the next step.

Step 3: 5-chloro-3-((1-(4-methoxybenzyl)-4-((4-methoxybenzyl)oxy)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile

To a solution of 5-chloro-3-((4-hydroxy-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile (9 g, 32.4 mmol) in DMF (300 mL) was added potassium carbonate (13.44 g, 97 mmol) followed by addition of 1-(chloromethyl)-4-methoxybenzene (12.69 g, 81 mmol) after 15 minute initial stirring at room temperature. The reaction mixture was heated at 80°C for 2 h, and then concentrated under reduced pressure. The residue was partitioned between ice water and EtOAc (3×). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica (0-40% EtOAc/P.E.) to afford the title compound. MS: 518.4 (M+1).

Step 4: 5-chloro-3-((4-hydroxy-1-(4-methoxybenzyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile

To a solution of 5-chloro-3-((1-(4-methoxybenzyl)-4-((4-methoxybenzyl)oxy)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile (10.2 g, 19.69 mmol) in DCM (85 mL) was added TFA (7.59 mL, 98 mmol) dropwise at 0°C and the reaction mixture was stirred at room temperature for 30 minutes, and then concentrated under reduced pressure. The residue was triturated with methanol and the solid was collected on top of a filter to afford the title compound. MS: 398.2 (M+1).

Step 5: 3-((4-hydroxy-1-(4-methoxybenzyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-2,5-dimethylbenzonitrile

To a solution of 5-chloro-3-((4-hydroxy-1-(4-methoxybenzyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile (1.45g, 3.64 mmol) in THF (15 mL) and water (2 mL) was added methylboronic acid (0.436 g, 7.29 mmol), potassium phosphate (2.321 g, 10.93 mmol). After purged with N₂, chloro(2-dicyclohexylphosphino-2',4',6'-tri-*i*-propyl-1,1'-biphenyl)(2'-amino-1,1'-biphenyl-2-yl) palladium(II) (0.287 g, 0.364 mmol) was added, then the reaction mixture was stirred at 100°C for 16 h. The reaction mixture was passed through a filter, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica (3% MeOH/ DCM.) to afford the title compound. MS: 378.2 (M+1).

Step 6: 3-((4-hydroxy-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-2,5-dimethylbenzonitrile

To a solution of 3-((4-hydroxy-1-(4-methoxybenzyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-2,5-dimethylbenzonitrile (1.0g, 2.65 mmol) in trifluoroacetic acid (10 mL, 130 mmol) at 0 °C, was added trifluoroacetic anhydride (5 mL, 35.4 mmol) and anisole (0.289 mL, 2.65 mmol). The reaction mixture was stirred at 100°C for 3 h, and then concentrated under reduced pressure. The residue was purified by column chromatography on silica (3% MeOH/DCM) to afford the title compound.

Step 7: 3-((4,6-dibromopyrimidin-5-yl)oxy)-2,5-dimethylbenzonitrile

To a solution of 3-((4-hydroxy-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-2,5-dimethylbenzonitrile (500 mg, 1.944 mmol) in ACN (10 mL) at 0 °C, was added phosphorus oxybromide (2229 mg, 7.77 mmol) followed by addition of triethylamine (0.542 mL, 3.89 mmol). The reaction mixture was stirred at 80°C for 16 h, and then concentrated under reduced pressure. The residue was partitioned between water and EtOAc. The organic layer was washed with saturated sodium bicarbonate aqueous solution, brine and dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica (7% EtOAc/P.E.) to afford the title compound.

Step 8: 3-((4-bromo-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-2,5-dimethylbenzonitrile

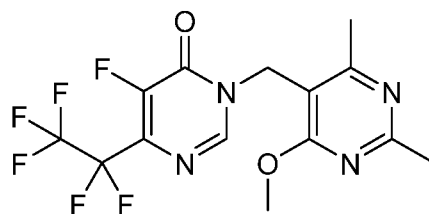
To a solution of 3-((4,6-dibromopyrimidin-5-yl)oxy)-2,5-dimethylbenzonitrile (530 mg, 1.384 mmol) in ACN (7 mL) and NMP (1.5 mL) was added potassium acetate (272 mg, 2.77 mmol). The reaction mixture was stirred at 80 °C for 16 h, and then concentrated under reduced pressure. The residue was partitioned between water and EtOAc. The organic layer was washed with water, brine and dried over anhydrous sodium sulfate, filtered and concentrated

under reduced pressure. The residue was purified by column chromatography on silica (50% EtOAc/P.E.) to afford the title compound. MS: 639.0 (2M+1).

Intermediate BC Section

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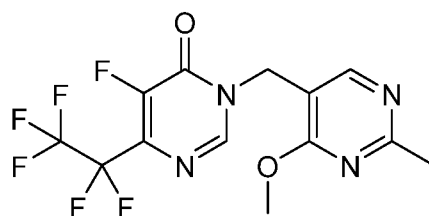
INTERMEDIATE BC01



5-fluoro-3-((4-methoxy-2,6-dimethylpyrimidin-5-yl)methyl)-6-(perfluoroethyl)pyrimidin-4(3H)-one

A mixture of 5-fluoro-6-(perfluoroethyl)pyrimidin-4(3H)-one, **B02** (420 mg, 1.81 mmol), potassium carbonate (625 mg, 4.52 mmol) and 5-(chloromethyl)-4-methoxy-2,6-dimethylpyrimidine, **C14** (405 mg, 2.17 mmol) in DMA (9 mL) was stirred at RT for 16 h. LC-MS showed good for the conversion of starting material to product. The mixture was filtered. The filtrate was taken up by EtOAc (200 mL), and washed with water (3×50 mL), brine (50 mL), dried over anhydrous MgSO₄, filtered and concentrated under reduced pressure. The residue was purified with column chromatography on silica (0-10% MeOH/DCM) to isolate the title compound. MS: 383.1 (M+1). ¹H NMR (600 MHz, DMSO-*d*₆) δ 8.79 (s, 1H), 4.86 (s, 2H), 2.35 (s, 3H), 2.27 (s, 3H), 2.18 (s, 3H).

INTERMEDIATE BC02



Methyl 5-fluoro-1-(4-methoxybenzyl)-6-oxo-1,6-dihydropyrimidine-4-carboxylate

A mixture of 5-fluoro-6-(perfluoroethyl)pyrimidin-4(3H)-one, **B02** (50 mg, 0.22 mmol), 5-(chloromethyl)-4-methoxy-2-methylpyrimidine, **C15** (55.8 mg, 0.32 mmol) and potassium carbonate (89 mg, 0.65 mmol) in NMP (431 μl) was stirred at 23 °C for 16 h. LC-MS showed reaction is complete. The reaction mixture was diluted with water and the precipitate was

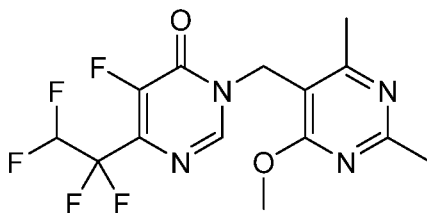
collected on top of a filter and washed with water (3×), air dried to afford the title compound.
MS: 369.1 (M+1).

The following intermediates in Table 11 were prepared under similar conditions
5 as the above synthetic procedure outlined in the synthesis of intermediate **BC02** using a
corresponding intermediate **B** that is described in section **B**.

TABLE 11

INT	Structure	IUPAC Name	MS (M+1)
BC03		5-fluoro-3-((4-methoxy-2-methylpyrimidin-5-yl)methyl)-6-(1,1,2,2-tetrafluoroethyl)pyrimidin-4(3H)-one	351.2
BC04		5-fluoro-3-((4-methoxy-2,6-dimethylpyrimidin-5-yl)methyl)-6-(trifluoromethyl)pyrimidin-4(3H)-one	333.2
BC05		5-fluoro-3-((4-methoxy-6-methylpyrimidin-5-yl)methyl)-6-(1,1,2,2-tetrafluoroethyl)pyrimidin-4(3H)-one	351.2

INTERMEDIATE BC06

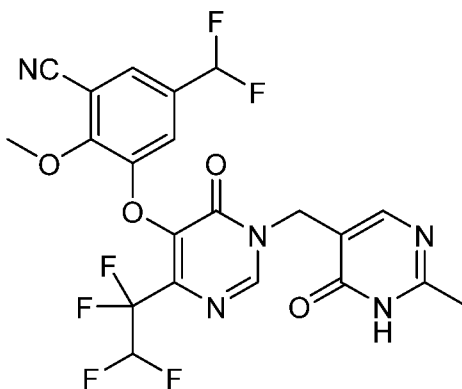


10

5-fluoro-3-((4-methoxy-2,6-dimethylpyrimidin-5-yl)methyl)-6-(1,1,2,2-tetrafluoroethyl)pyrimidin-4(3H)-one

A mixture of 5-fluoro-6-(1,1,2,2-tetrafluoroethyl)pyrimidin-4(3H)-one, **B01** (123 mg, 0.57 mmol), 5-(chloromethyl)-4-methoxy-2,6-dimethylpyrimidine, **C15** (107 mg, 0.57 mmol) and potassium carbonate (238 mg, 1.72 mmol) in NMP (1147 μ l) was stirred at 23 °C for 16 h. LC-MS showed the reaction is complete. The reaction mixture was filtered and purified with reverse phase HPLC (ACN/water with 0.1% TFA modifier) to afford the title compound. MS: 365.1 (M+1).

EXAMPLE 1



5-(difluoromethyl)-2-methoxy-3-((1-((2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile

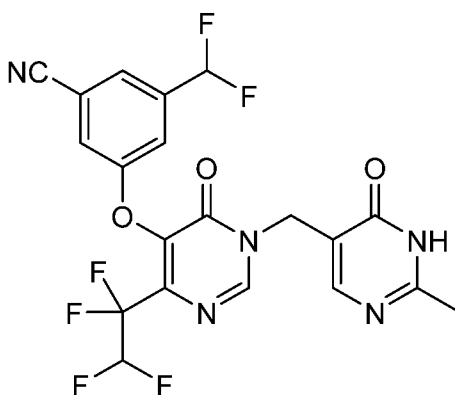
Step 1: 5-(difluoromethyl)-2-methoxy-3-((1-((4-((4-methoxybenzyl)oxy)-2-methylpyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile

To a solution of 5-(difluoromethyl)-2-methoxy-3-((6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile, **AB18** (46 mg, 0.12 mmol) in DMF (1 mL) was added 5-(chloromethyl)-4-((4-methoxybenzyl)oxy)-2-methylpyrimidine, **C15** (48.9 mg, 0.175 mmol), K₂CO₃ (48.5 mg, 0.351 mmol) and LiBr (10.16 mg, 0.117 mmol). The resulting reaction mixture was stirred at 50 °C for 2 h. LC-MS showed the reaction was complete. The reaction was concentrated under reduced pressure. The residue was purified by column chromatography on silica (66% EtOAc/P.E.) to give the title compound. MS: 634.4 (M-1).

Step 2: 5-(difluoromethyl)-2-methoxy-3-((1-((2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile

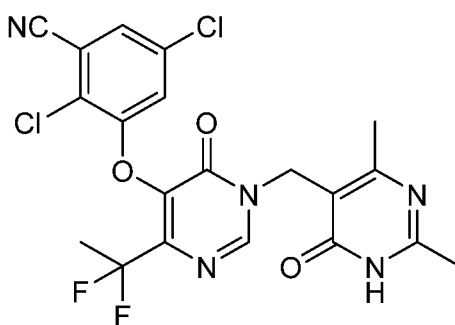
To a solution of 5-(difluoromethyl)-2-methoxy-3-((1-((4-((4-methoxybenzyl)oxy)-2-methylpyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile (15 mg, 0.024 mmol) in DCM (1 mL) was added TFA (1 mL, 12.98 mmol).

And the resulting mixture was stirred under N₂ at 25 °C for 1 h. LC-MS showed the starting material was consumed completely. The reaction mixture was concentrated under reduced pressure. The residue was purified by reverse phase HPLC (ACN/water with 0.1% TFA modifier) to afford the title compound. MS: 516.2 (M+1). ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.75 (s, 1 H), 7.90 (s, 1 H), 7.74 (s, 1 H), 7.40 (s, 1 H), 6.69 - 7.03 (m, 2 H), 4.85 (s, 2 H), 4.02 (s, 3 H), 2.26 (s, 3 H).

EXAMPLE 2

3-(difluoromethyl)-5-((1-((2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile

This compound was prepared in an analogous manner to that described above for the synthesis of **Example 1** using an appropriate intermediate **AB01** and intermediate **C15**. MS: 486 (M+1)

EXAMPLE 3

2,5-dichloro-3-((4-(1,1-difluoroethyl)-1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile

Step 1: 5-chloro-3-((4-(1,1-difluoroethyl)-1-((4-methoxy-2,6-dimethylpyrimidin-5-yl)methyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile

A mixture of 2, 5-dichloro-3-((6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1, 6-dihydropyrimidin-5-yl)oxy) benzonitrile, **AB01** (30 mg, 0.079 mmol), 5-(chloromethyl)-4-methoxy-2,6-dimethylpyrimidine, **C14** (29.3 mg, 0.157 mmol), lithium bromide (13.64 mg, 0.157 mmol) and K₂CO₃ (76 mg, 0.550 mmol) in DMF (4 mL) was stirred at 50 °C for 2 h. TLC shows that the reaction was complete. The reaction mixture was diluted with saturated NaHCO₃ aqueous solution (20 mL) and extracted with EtOAc (2×10 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under the reduced pressure to afford the title compound. MS: 532 (M+1).

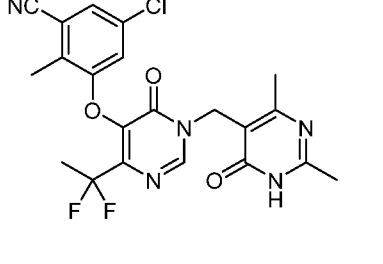
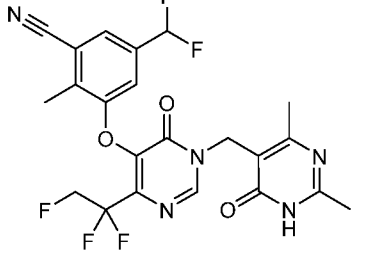
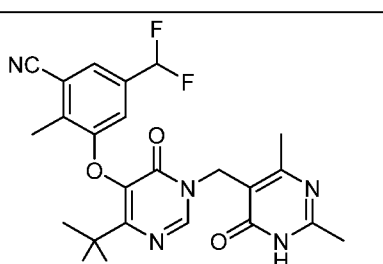
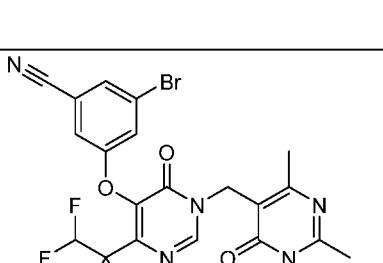
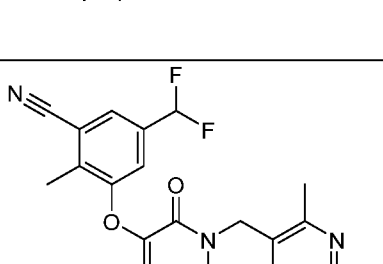
Step 2: 2,5-dichloro-3-((4-(1,1-difluoroethyl)-1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile

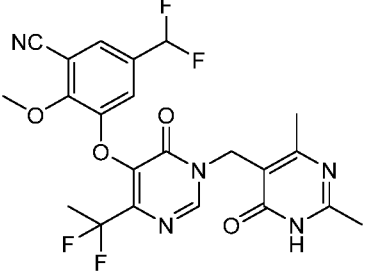
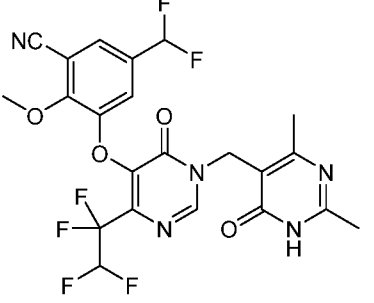
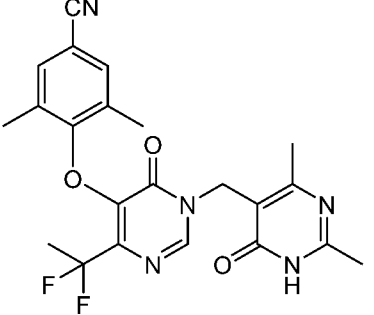
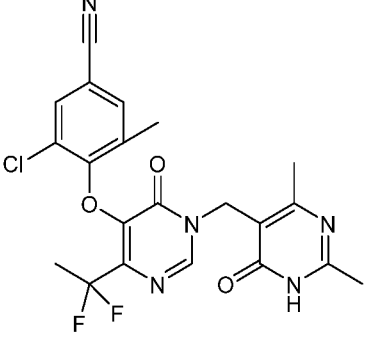
To a solution of 2, 5-dichloro-3-((4-(1,1-difluoroethyl)-1-((4-methoxy-2, 6-dimethylpyrimidin-5-yl) methyl)-6-oxo-1, 6-dihydropyrimidin-5-yl)oxy) benzonitrile (40 mg, 0.081 mmol) in ACN (3.0 mL) was added KI (40.1 mg, 0.242 mmol) and TMS-Cl (0.031 mL, 0.242 mmol). The resulting mixture was stirred at 70 °C for 1.5 h. LC-MS showed the reaction was completed. The reaction mixture was diluted with water (5 mL), and extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtrated and concentrated under reduced pressure. The residue was purified by reverse phase HPLC (ACN/water with 0.1% TFA as modifier) to afford the title compound. MS: 548.2 (M+1). ¹H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.70 (s, 1 H) 7.37 (d, *J*=2.20 Hz, 1 H) 6.79 (d, *J*=2.21 Hz, 1 H) 5.02 (s, 2 H) 2.60 (s, 3 H) 2.50 (s, 3 H) 1.97 (t, *J*=18.85 Hz, 3 H).

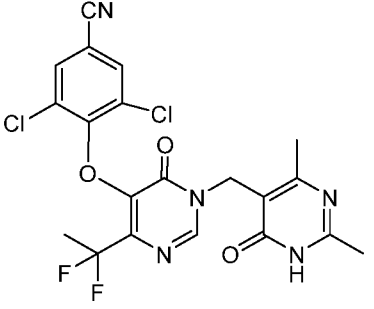
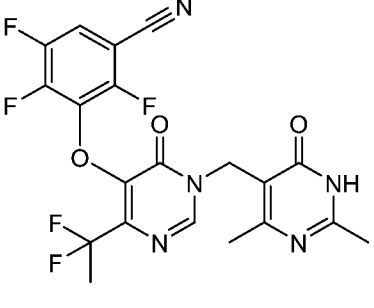
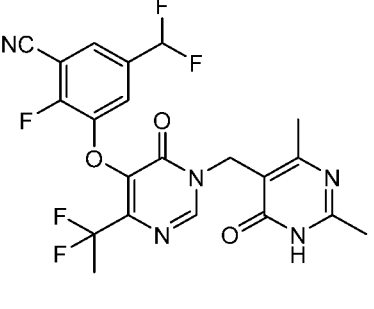
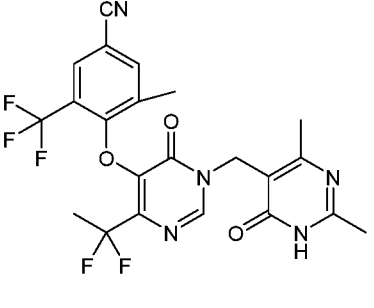
The following examples in Table 12 were prepared in an analogous manner as that described above for the synthesis of **Example 3** using an appropriate intermediate **AB** and intermediate **C**.

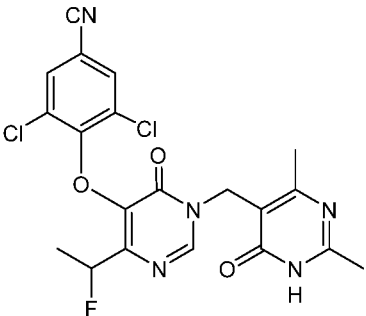
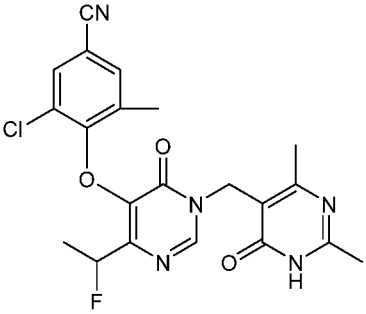
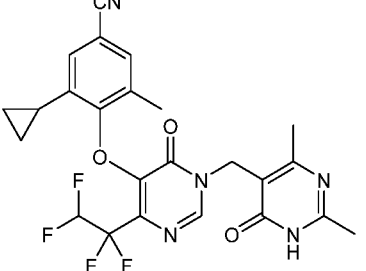
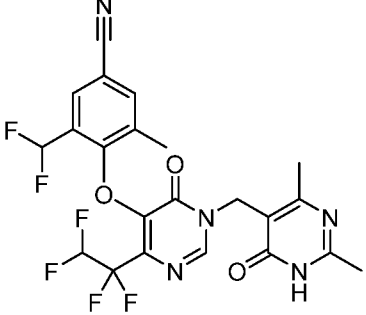
TABLE 12

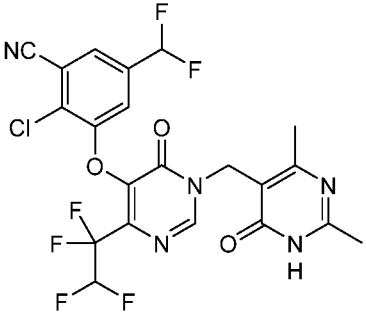
Ex# (AB#, C#)	Structure	IUPAC Name	MS (M+1)
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4 (AB01, C14)		5-chloro-3-((4-(1,1-difluoroethyl)-1- ((2,4-dimethyl-6-oxo-1,6- dihydropyrimidin-5-yl)methyl)-6-oxo- 1,6-dihydropyrimidin-5-yl)oxy)-2- methylbenzonitrile	462
5 (AB04, C14)		5-(difluoromethyl)-3-((1-((2,6- dimethyl-4-oxo-4,5-dihydropyrimidin- 5-yl)methyl)-6-oxo-4-(1,1,2- trifluoroethyl)-1,6-dihydropyrimidin-5- yl)oxy)-2-methylbenzonitrile	496.2
6 (AB03, C14)		3-((4-(1,1-difluoroethyl)-1-((2,4- dimethyl-6-oxo-1,6-dihydropyrimidin- 5-yl)methyl)-6-oxo-1,6- dihydropyrimidin-5-yl)oxy)-5- (difluoromethyl)-2-methylbenzonitrile	478
7 (AB13, C14)		3-bromo-5-((1-((2,4-dimethyl-6-oxo- 1,6-dihydropyrimidin-5-yl)methyl)-6- oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6- dihydropyrimidin-5-yl)oxy)benzonitrile	529 and 530
8 (AB05, C14)		5-(difluoromethyl)-3-((1-((2,4- dimethyl-6-oxo-1,6-dihydropyrimidin- 5-yl)methyl)-6-oxo-4-(trifluoromethyl)- 1,6-dihydropyrimidin-5-yl)oxy)-2- methylbenzonitrile	482.1

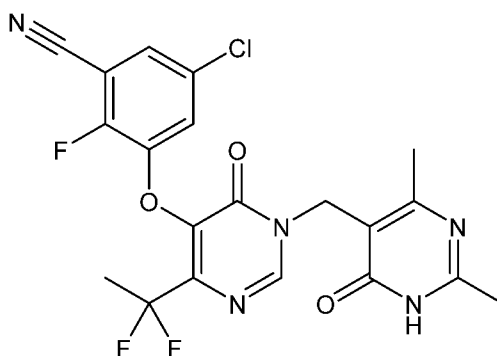
9 (AB20, C14)		3-((4-(1,1-difluoroethyl)-1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-5-(difluoromethyl)-2-methoxybenzonitrile	494.0
10 (AB18, C14)		5-(difluoromethyl)-3-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-methoxybenzonitrile	530.2
11 (AB17, C14)		4-((4-(1,1-difluoroethyl)-1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-3,5-dimethylbenzonitrile	442.1
12 (AB21, C14)		3-chloro-4-((4-(1,1-difluoroethyl)-1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-5-methylbenzonitrile	462.2

13 (AB19, C14)		3,5-dichloro-4-((4-(1,1-difluoroethyl)-1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile	482
14 (AB23, C14)		3-((4-(1,1-difluoroethyl)-1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-2,4,5-trifluorobenzonitrile	468.1
15 (AB15, C14)		3-((4-(1,1-difluoroethyl)-1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-5-(difluoromethyl)-2-fluorobenzonitrile	482.1
16 (AB22, C14)		4-((4-(1,1-difluoroethyl)-1-((4-hydroxy-2,6-dimethylpyrimidin-5-yl)methyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-3-methyl-5-(trifluoromethyl)benzonitrile	496.2

17 (AB25, C14)		(S) or (R)-3,5-dichloro-4-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-4-(1-fluoroethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile <i>single enantiomer (faster eluting isomer A)</i>	464.0
18 (AB28, C14)		(S) or (R)-3-chloro-4-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-4-(1-fluoroethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-5-methylbenzonitrile <i>single enantiomer (faster eluting isomer A)</i>	444.2
19 (AB30, C14)		3-cyclopropyl-4-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-5-methylbenzonitrile	504.0
20 (AB31, C14)		3-(difluoromethyl)-4-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-5-methylbenzonitrile	514

21 (AB14, C14)		2-chloro-5-(difluoromethyl)-3-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile	534.2
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EXAMPLE 22



5 5-(difluoromethyl)-3-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-4-(1-fluoroethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile

Step 1: 5-Chloro-3-((4-(1,1-difluoroethyl)-1-((4-methoxy-2,6-dimethylpyrimidin-5-yl)methyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-2-fluorobenzonitrile

To a stirred solution of 5-chloro-3-((4-(1,1-difluoroethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-2-fluorobenzonitrile, **AB34** (50 mg, 0.152 mmol) and 5-(chloromethyl)-4-methoxy-2,6-dimethylpyrimidine, **C14** (31.1 mg, 0.167 mmol) in DMF (758 μ L), was added K_2CO_3 (41.9 mg, 0.303 mmol). The resulting mixture was stirred at RT overnight. The mixture was filtered to give the title compound, which was used directly in the next step.

10 Step 2: 5-Chloro-3-((4-(1,1-difluoroethyl)-1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-2-fluorobenzonitrile

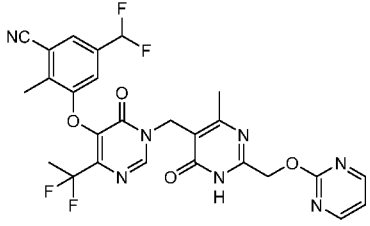
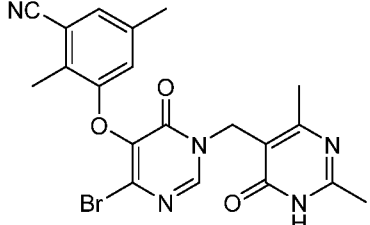
To a solution of 5-Chloro-3-((4-(1,1-difluoroethyl)-1-((4-methoxy-2,6-dimethylpyrimidin-5-yl)methyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-2-fluorobenzonitrile

(72.9 mg, 0.152 mmol) in NMP (758 μ L), was added pyridine hydrochloride (88 mg, 0.76 mmol). The resulting mixture was heated at 120 $^{\circ}$ C in a microwave oven for 20 min. LC-MS showed desired product. The reaction mixture was diluted with water (100 μ L) and DMSO (300 μ L) and purified by reverse phase HPLC (ACN/water with 0.1% TFA as modifier) to afford the title compound. MS: 466.0 (M+1). ^{1} H NMR (600 MHz, DMSO- d_6): δ 8.72 (s, 1H), 7.81 (dd, J = 4.3, 2.3 Hz, 1H), 7.61 (dd, J = 7.4, 2.3 Hz, 1H), 4.90 (s, 2H), 2.35 (s, 3H), 2.27 (s, 3H), 1.92 (t, J = 19.6 Hz, 3H).

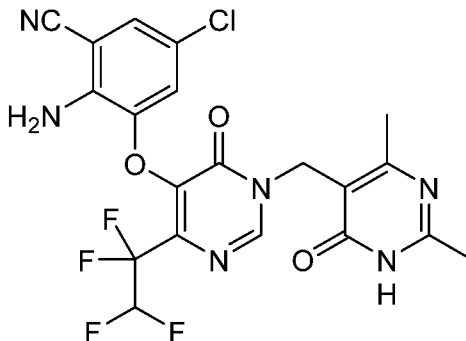
The following examples in Table 13 were prepared in an analogous manner to that described above for the synthesis of **Example 22** using an appropriate intermediate AB and intermediate C.

TABLE 13

Ex# (AB#, C#)	Structure	IUPAC Name	MS (M+1)
23 (AB08, C14)		3-((4-(1,1-difluoroethyl)-1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-5-(difluoromethyl)benzonitrile	464.1
24 (AB34, C25)		5-chloro-3-((4-(1,1-difluoroethyl)-1-((4-methyl-6-oxo-2-((pyrimidin-2-yloxy)methyl)-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-2-fluorobenzonitrile	559.9

25 (AB03, C25)		3-((4-(1,1-difluoroethyl)-1-((4-methyl-6-oxo-2-((pyrimidin-2-yl)oxy)methyl)-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-5-(difluoromethyl)-2-methylbenzonitrile	572.0
26 (AB35, C14)		3-((4-bromo-1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-2,5-dimethylbenzonitrile	458.1

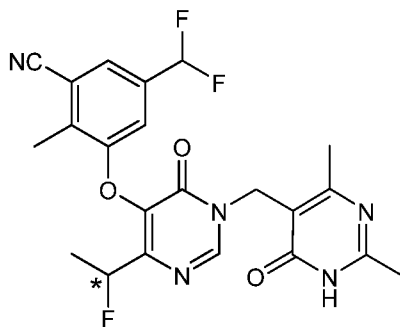
EXAMPLE 27



2-amino-5-chloro-3-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile

A solution of 5-chloro-3-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-fluorobenzonitrile, **Example 23** (800 mg, 1.594 mmol) in EtOH (280 mL) was stirred at 60 °C under NH₃ for 30 h, and then concentrated by blowing under N₂ to give the crude residue. The residue was purified by reverse phase HPLC (ACN/water with 0.1% TFA as modifier) to afford the title compound. MS: 499.1 (M+1).

EXAMPLES 28 (isomer A) and 29 (isomer B)



(S)-5-(difluoromethyl)-3-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-4-(1-fluoroethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile, and

5 (R)-5-(difluoromethyl)-3-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-4-(1-fluoroethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile

Step 1: 5-(difluoromethyl)-3-((4-(1-fluoroethyl)-1-((4-methoxy-2,6-dimethylpyrimidin-5-yl)methyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile

To a stirred solution of 5-(difluoromethyl)-3-((4-(1-fluoroethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile, **AB27** (200 mg, 0.619 mmol) in DMF (2 mL) was added 5-(chloromethyl)-4-methoxy-2,6-dimethylpyrimidine, **C14** (115 mg, 0.619 mmol), K₂CO₃ (171 mg, 1.237 mmol) and lithium bromide (53.7 mg, 0.619 mmol). The resulting mixture was stirred at 25 °C for 1 h. TLC (50% EtOAc/P.E.) showed the reaction was complete. The reaction mixture was diluted with water (20 mL) and extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by prepative TLC plates (50% EtOAc/P.E.) to give a racemic mixture of the title compound. MS: 474.1, (M+1).

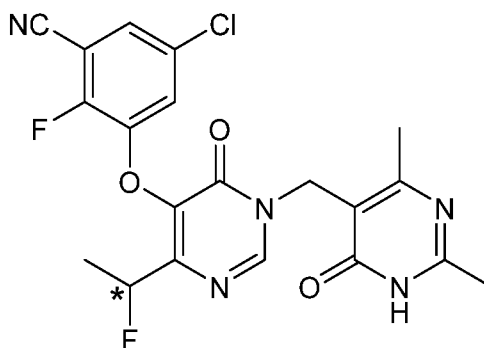
Step 2: 5-(difluoromethyl)-3-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-4-(1-fluoroethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile

20 To a stirred solution of 5-(difluoromethyl)-3-((4-(1-fluoroethyl)-1-((4-methoxy-2,6-dimethylpyrimidin-5-yl)methyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile (180 mg, 0.380 mmol) in ACN (4 mL) was added KI (189 mg, 1.141 mmol) and TMS-Cl (0.146 mL, 1.141 mmol). The resulting reaction mixture was stirred at 70 °C for 12 h. TLC (66% EtOAc/P.E.) showed the reaction was complete. The reaction mixture was concentrated under

reduced pressure. The residue was purified by reverse phase HPLC (ACN/water with 0.1% TFA as modifier) to afford a racemate of the title compound. MS: 460.2 (M+1).

The racemic mixture was purified by chiral SFC (IC-H column, 25% EtOH/CO₂ with 0.1% NH₄OH as modifier) to afford **Example 28 isomer A** (faster eluting): MS: 460.2 (M+1),
 5 and **Example 29 isomer B** (slower eluting): MS: 460.2 (M+1).

EXAMPLES 30 (isomer A) and 31 (isomer B)



(S)-5-chloro-3-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-4-(1-fluoroethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-2-fluorobenzonitrile, and

10 (R)-5-chloro-3-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-4-(1-fluoroethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-2-fluorobenzonitrile

Step 1: 5-chloro-2-fluoro-3-((4-(1-fluoroethyl)-1-((4-methoxy-2,6-dimethylpyrimidin-5-yl)methyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile

15 To a solution of 5-chloro-2-fluoro-3-((4-(1-fluoroethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile, **AB24** (152 mg, 0.488 mmol) in DMF (5 mL), was added K₂CO₃ (202 mg, 1.46 mmol), lithium bromide (85 mg, 0.98 mmol), and then 5-(chloromethyl)-4-methoxy-2,6-dimethylpyrimidine, **C14** (202 mg, 0.975 mmol). The resulting reaction mixture was stirred at 20 °C for 30 min. TLC (33% EtOAc/P.E.) and LC-MS showed the reaction was complete. The
 20 mixture was diluted with water (5.0 mL), and extracted with EtOAc (3×5 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give the title compound. MS: 462.2 (M+1).

Step 2: 5-chloro-2-fluoro-3-((4-(1-fluoroethyl)-1-((4-hydroxy-2,6-dimethylpyrimidin-5-yl)methyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile

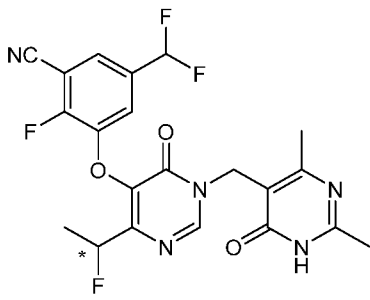
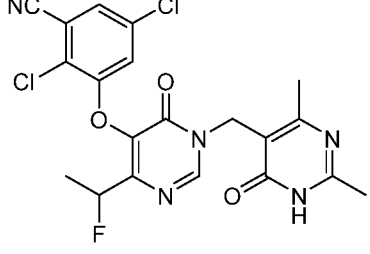
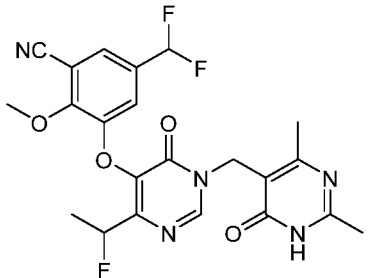
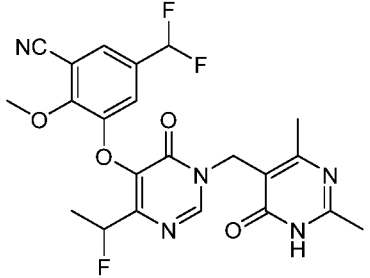
To a solution of 5-chloro-2-fluoro-3-((4-(1-fluoroethyl)-1-((4-methoxy-2,6-dimethylpyrimidin-5-yl)methyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile (150 mg, 0.325 mmol) in ACN (3 mL), was added KI (67.9 mg, 0.409 mmol) and TMS-Cl (0.136 mL, 1.065 mmol). The resulting reaction mixture was stirred at 70 °C for 5 h. TLC (20%

EtOAc/P.E.) showed the reaction was complete. The reaction mixture was concentrated under reduced pressure. Then residue was purified by reverse phase HPLC (ACN/water with 0.1% TFA as modifier) to give racemic mixture of the title compounds. MS: 448.2 (M+1). The mixture of the two stereoisomers was purified by chiral SFC (IC-H, 35% IPA/CO₂) to afford **Example 30 isomer A** (faster eluting): MS: 448.2 (M+1), ¹H NMR (400MHz, DMSO-d₆) δ 8.67 (s, 1H), 7.81 (br d, J=2.3 Hz, 1H), 7.55 - 7.46 (m, 1H), 5.82 - 5.61 (m, 1H), 4.87 (br s, 2H), 2.33 (s, 3H), 2.23 (s, 3H), 1.59 - 1.47 (m, 3H), and **Example 31 isomer B** (slower eluting): MS: 448.2 (M+1), ¹H NMR (400MHz, DMSO-d₆) δ 8.67 (s, 1H), 7.81 (dd, J=2.3, 4.4 Hz, 1H), 7.51 (dd, J=2.3, 7.3 Hz, 1H), 5.83 - 5.62 (m, 1H), 4.87 (br s, 2H), 2.33 (s, 3H), 2.23 (s, 3H), 1.59 - 1.45 (m, 3H).

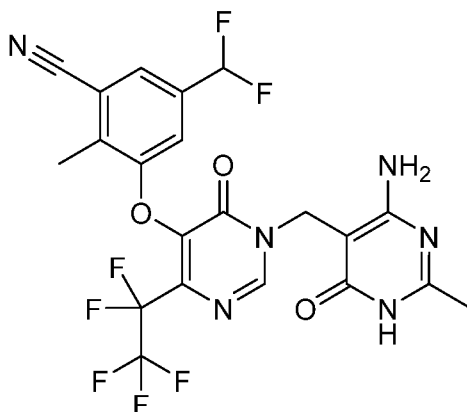
The following compounds in Table 14 were each prepared as a racemate followed by purification to obtain the noted isomer(s) in an analogous manner to that described above for the synthesis of **Example 30** using, an appropriate intermediate AB and intermediate C which were described in the intermediate session.

TABLE 14

Ex# (AB#, C#)	Structure	IUPAC Name	MS (M+1)
32 (AB33, C14)		(S) or (R)-5-(difluoromethyl)-3-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-4-(1-fluoroethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-2-fluorobenzonitrile single enantiomer (faster eluting isomer A)	464.1

33 (AB33, C14)		(<i>R</i>) or (<i>S</i>)-5-(difluoromethyl)-3-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-4-(1-fluoroethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-2-fluorobenzonitrile single enantiomer (slower eluting isomer B)	464.1
34 (AB26, C14)		(<i>S</i>) or (<i>R</i>)-2,5-dichloro-3-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-4-(1-fluoroethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile single enantiomer (faster eluting isomer A)	464.0
35 (AB32, C14)		(<i>S</i>) or (<i>R</i>)-5-(difluoromethyl)-3-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-4-(1-fluoroethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-2-methoxybenzonitrile single enantiomer (faster eluting isomer A)	476.0
36 (AB32, C14)		(<i>R</i>) or (<i>S</i>)-5-(difluoromethyl)-3-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-4-(1-fluoroethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-2-methoxybenzonitrile single enantiomer (slower eluting isomer B)	476.0

EXAMPLE 37



3-((1-((4-amino-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-5-(difluoromethyl)-2-methylbenzonitrile

Step 1: 3-((1-((4-(bis(4-methoxybenzyl)amino)-6-methoxy-2-methylpyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-5-(difluoromethyl)-2-methylbenzonitrile

To a chilled (0°C) solution of 5-(difluoromethyl)-2-methyl-3-((6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile, **AB06** (100 mg, 0.253 mmol) and (4-(Bis(4-methoxybenzyl)amino)-6-methoxy-2-methylpyrimidin-5-yl)methanol, **C13** (104 mg, 0.253 mmol) in DCM (1265 µl), was added triphenylphosphine (66.4 mg, 0.253 mmol) and DIAD (49.2 µl, 0.253 mmol). The resulting solution was stirred at 23 °C for 16 h, then purified directly by column chromatography on silica (0-50% EtOAc/hexanes) to afford title compound. MS: 787.2 (M+1).

Step 2: 3-((1-((4-amino-6-methoxy-2-methylpyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-5-(difluoromethyl)-2-methylbenzonitrile

3-((1-((4-(bis(4-methoxybenzyl)amino)-6-methoxy-2-methylpyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-5-(difluoromethyl)-2-methylbenzonitrile (130 mg, 0.165 mmol) was dissolved in TFA (2 mL) and was heated to 100 °C for 1 h. The solution was concentrated under reduced pressure. The residue was further dried via azotropic evaporation with toluene to isolate the title compound. MS: 547.1 (M+1).

Step 3: 3-((1-((4-amino-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-5-(difluoromethyl)-2-methylbenzonitrile

To a chilled (0 °C) solution of 3-((1-((4-amino-6-methoxy-2-methylpyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-5-(difluoromethyl)-2-

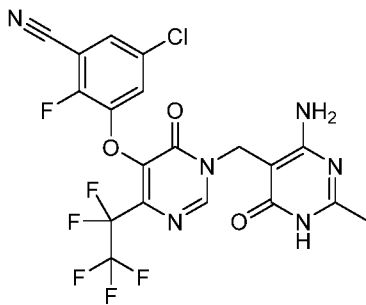
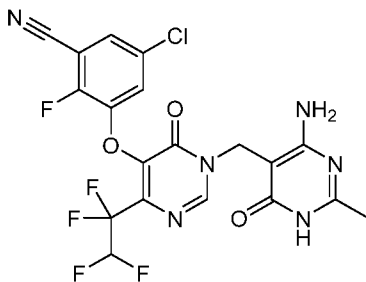
methylbenzonitrile (90 mg, 0.165 mmol) in ACN (824 μ L), was added TMS-I (448 μ L, 3.29 mmol). The resulting reaction mixture was stirred at 23 $^{\circ}$ C for 1 h. The reaction is neutralized with Na₂SO₃ (500 μ L), then concentrated under reduced pressure. The residue was purified by reverse phase HPLC (ACN/water with 0.05% NH₄OH modifier) to afford the title compound.

5 MS: 410.3 (M+1). ¹H NMR (600 MHz, DMSO-*d*₆) δ 11.66 (s, 1H), 8.57 (s, 1H), 7.74 (s, 1H), 7.35 (s, 1H), 6.88 (t, J = 55.3 Hz, 1H), 6.58 (s, 2H), 4.74 (s, 2H), 3.28 (s, 3H), 2.10 (s, 3H).

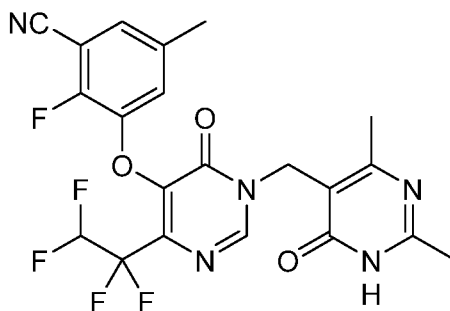
The following examples in Table 15 were prepared in an analogous manner to that described in **Example 37** with appropriate intermediate AB described in the intermediate section.

10

TABLE 15

Ex# (AB#, C#)	Structure	IUPAC Name	MS (M+1)
38 (AB12, C13)		3-((1-((4-amino-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-5-chloro-2-fluorobenzonitrile	521.1
39 (AB10, C13)		3-((1-((4-amino-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-5-chloro-2-fluorobenzonitrile	503.1

EXAMPLE 40



3-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-fluoro-5-methylbenzonitrile

Step 1: 5-chloro-2-fluoro-3-((1-((4-methoxy-2,6-dimethylpyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile

To a mixture of 5-chloro-2-fluoro-3-((6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile, **AB10** (153 mg, 0.418 mmol), K₂CO₃ (133 mg, 0.964 mmol) and LiBr (27.9 mg, 0.321 mmol) in DMF (3 mL) was added 5-(chloromethyl)-4-methoxy-2,6-dimethylpyrimidine, **C14** (60 mg, 0.321 mmol). The resulting reaction mixture was stirred at 20 °C for 3 h, and then concentrated under reduced pressure. The residue was purified by column chromatography on silica (0-33% EtOAc/P.E.) to give the title compound. ¹HNMR (400 MHz, DMSO-*d*₆) δ 8.70 (s, 1 H) 7.85 (dd, *J*=4.82, 2.63 Hz, 1 H) 7.69 (dd, *J*=7.24, 2.41 Hz, 1 H) 6.68 - 7.01 (m, 2 H) 5.06 (s, 2 H) 3.88 (s, 3 H) 2.48 (br s, 3 H) 2.45 (s, 3 H).

Step 2: 2-fluoro-3-((1-((4-methoxy-2,6-dimethylpyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-5-methylbenzonitrile

To a mixture of 5-chloro-2-fluoro-3-((1-((4-methoxy-2,6-dimethylpyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile (180 mg, 348.96 μmol) in 1,4-dioxane (4 mL) and H₂O (0.5 mL) were added K₂CO₃ (144.68 mg, 1.05 mmol), 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (131.42 mg, 1.05 μmol), X-Phos (83.18 mg, 174.48 μmol) and Pd(OAc)₂ (7.83 mg, 34.9 μmol). The resulting mixture was stirred at 110 °C under N₂ for 2 h, and then purified by column chromatography on silica (0-33% EtOAc/P.E.) to give the title compound. MS: 496.2 (M+1).

Step 3: 3-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-fluoro-5-methylbenzonitrile

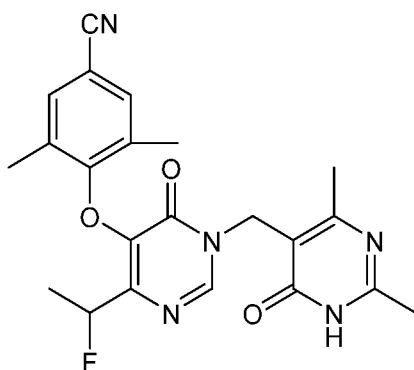
To a solution of 2-fluoro-3-((1-((4-methoxy-2,6-dimethylpyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-5-methylbenzonitrile (100 mg, 201.85 μmol) in ACN (5 mL) were added TMS-Cl (65.79 mg, 605.56 μmol) and KI (100.52 mg, 605.56 μmol). The resulting reaction mixture was stirred at 70 °C for 2 h, and then concentrated under reduced pressure. The residue was purified by reverse phase HPLC (ACN/water with 0.1% TFA as modifier) to afford the title compound. MS: 482.1 (M+1). ^1H NMR (400 MHz, DMSO- d_6) δ 8.77 (s, 1 H) 7.42 (br d, J=3.75 Hz, 1 H) 7.21 - 7.27 (m, 1 H) 6.70 - 7.01 (m, 1 H) 4.91 (s, 2 H) 2.35 (s, 3 H) 2.28 (s, 3 H) 2.23 (s, 3 H).

The following examples in Table 16 were prepared in an analogous manner to that described in **Example 40** with an appropriate intermediate AB described in the intermediate section.

TABLE 16

Ex# (AB#, C#)	Structure	IUPAC Name	MS (M+1)
41 (AB34, C14)		3-((4-(1,1-difluoroethyl)-1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-2-fluoro-5-methylbenzonitrile	446.2
42 (AB10, C14)		3-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-5-ethyl-2-fluorobenzonitrile	496.2

EXAMPLE 43 (isomer A)



(S) or (R)-4-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-4-(1-fluoroethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-3,5-dimethylbenzonitrile

Step 1: 4-((4-acetyl-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-3,5-dimethylbenzonitrile

5 To a solution of 4-((4-acetyl-1-(4-methoxybenzyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-3,5-dimethylbenzonitrile, **AB16** (650 mg, 1.45 mmol) in TFA (5 mL, 64.9 mmol) was added TFAA (2.5 mL, 17.70 mmol). The resulting reaction mixture was stirred at 110 °C for 6 h. Then the reaction mixture was concentrated under reduced pressure, then basified to pH ~9 with saturated NaHCO₃ aq. solution (10.0 mL), and extracted with EtOAc (3×20 mL). The
10 combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtrated and concentrated under reduced pressure to give the title compound. MS: 284.1 (M+1), 589.1 (2M+23), and used directly without further purification.

Step 2: 4-((4-acetyl-1-((4-methoxy-2,6-dimethylpyrimidin-5-yl)methyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-3,5-dimethylbenzonitrile

15 To a solution of 4-((4-acetyl-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-3,5-dimethylbenzonitrile (500 mg)(crude), lithium bromide (307 mg, 3.53 mmol) in DMA (5 mL) was added 5-(chloromethyl)-4-methoxy-2,6-dimethylpyrimidine, **C14** (366 mg, 1.765 mmol) and K₂CO₃ (488 mg, 3.53 mmol). The resulting reaction mixture was stirred at 20 °C for 30 min. Upon completion of the reaction, water (5.0 mL) was added. And the reaction mixture was
20 extracted with EtOAc (3×5 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtrated and concentrated under reduced pressure. The residue was purified with preparative TLC plates (10% MeOH/DCM) to give the title compound.

Step 3: 4-((4-(1-hydroxyethyl)-1-((4-methoxy-2,6-dimethylpyrimidin-5-yl)methyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-3,5-dimethylbenzonitrile

To a solution of 4-((4-acetyl-1-((4-methoxy-2, 6-dimethylpyrimidin-5-yl) methyl)- 6 -oxo-1, 6-dihydropyrimidin-5-yl)oxy)-3,5-dimethylbenzonitrile (200 mg, 0.438 mmol) in MeOH (1.0 mL) was added 1M Zn(BH₄)₂ solution in THF (0.110 mL, 0.110 mmol) at -10-0°C. The resulting reaction mixture was stirred at -10-0°C for 0.5 h. TLC (10% MeOH/DCM) showed the reaction was complete. The reaction mixture was diluted with water (5 mL) and extracted with EtOAc (4×10 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtrated and concentrated under reduced pressure to afford the title compound.

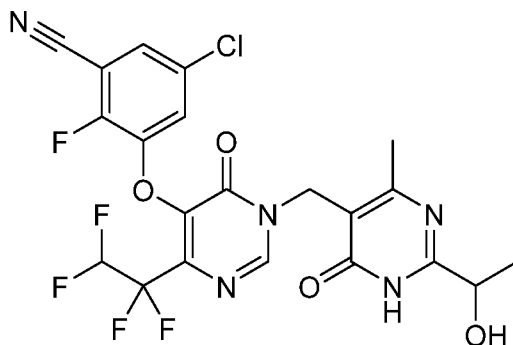
Step 4: 4-((4-(1-fluoroethyl)-1-((4-methoxy-2,6-dimethylpyrimidin-5-yl)methyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-3,5-dimethylbenzonitrile

To a solution of 4-((4-(1-hydroxyethyl)-1-((4-methoxy-2, 6-dimethylpyrimidin-5-yl)methyl)- 6 -oxo-1, 6-dihydropyrimidin-5-yl) oxy)-3,5-dimethylbenzonitrile (130 mg, 0.269 mmol) in DCM (5 mL) was added DAST (0.082 mL, 0.618 mmol) at 0 °C and the resulting mixture was stirred at 0 °C for 1 h. TLC (10% MeOH/DCM) and showed the reaction was complete. The reaction mixture was diluted with water (5 mL), and extracted with DCM (3×10 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtrated and concentrated under reduced pressure to give the title compound. MS: 438.1 (M+1).

Step 5: 4-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-4-(1-fluoroethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-3,5-dimethylbenzonitrile

To a solution of 4-((4-(1-fluoroethyl)-1-((4-methoxy-2, 6-dimethylpyrimidin-5-yl)methyl)- 6 -oxo-1, 6-dihydropyrimidin-5-yl) oxy)-3,5-dimethylbenzonitrile (150 mg, 0.261 mmol) in ACN (2 mL) was added KI (216 mg, 1.303 mmol) and TMS-Cl (0.167 mL, 1.303 mmol). The resulting reaction mixture was stirred at 70 °C for 1 h, and then concentrated under reduced pressure. The residue was purified by reverse phase HPLC (ACN/water with 0.1% TFA as modifier) to give racemic mixture of the title compound. MS: 424.1 (M+1). The racemic mixture was purified by chiral SFC (IC-H column, 40% IPA/CO₂ with 0.1% NH₄OH as modifier) to give **Example 43 isomer A** (faster eluting) MS: 424.1 (M+1). ¹H NMR (400 MHz, DMSO-*d*₆): δ 12.44(s, 1H), 8.42(s, 1H), 7.49(d, J=7.24, 2H), 6.06(d, J=6.00, 0.5H), 5.94(d, J=6.80, 0.5H) 4.77(s, 2H). 2.22(d, J=10.4, 6H), 2.06(s, J=7.2, 6H), 1.58(m, 3H).

EXAMPLE 44 (isomer B)



(S) or (R)-5-chloro-2-fluoro-3-((1-((2-(1-hydroxyethyl)-4-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-2-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,2-dihydropyridin-3-yl)oxy)benzonitrile

Step 1: 3-((1-((2-acetyl-4-methoxy-6-methylpyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-5-chloro-2-fluorobenzonitrile

To a stirred solution of 5-chloro-2-fluoro-3-((6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile, **AB10** (307 mg, 0.839 mmol) in DMF (10 mL) was added K₂CO₃ (193 mg, 1.398 mmol), lithium bromide (91 mg, 1.048 mmol) and 1-(5-(chloromethyl)-4-methoxy-6-methylpyrimidin-2-yl)ethanone, **C21** (150 mg, 0.00 mmol). And the resulting mixture was stirred at 20 °C for 16 h. TLC (50% EtOAc/P.E.) showed the completion of the reaction. The reaction mixture was diluted with water (15 mL) and extracted with EtOAc (3×20mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica (10-66% EtOAc/P.E.) to afford the title compound. MS: 544 (M+1).

Step 2: 5-chloro-2-fluoro-3-((1-((2-(1-hydroxyethyl)-4-methoxy-6-methylpyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile

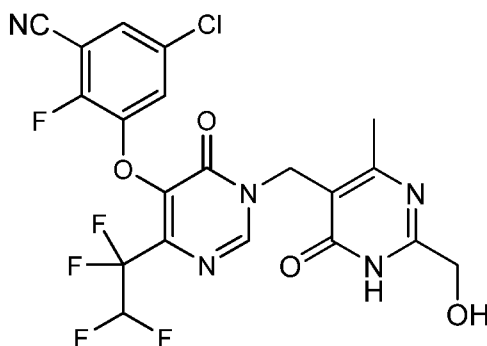
To a stirred solution of 3-((1-((2-acetyl-4-methoxy-6-methylpyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-5-chloro-2-fluorobenzonitrile (95 mg, 0.175 mmol) in DCM (5 mL) was added a solution of zinc borohydride (0.175 mL, 0.175 mmol) in DCM (1 mL). And the resulting mixture was stirred at 20 °C for 5 min. TLC (25% EtOAc/P.E.) showed the completion of the reaction. The reaction mixture was quenched with 1N HCl aqueous solution (5 mL) and water (20 mL), extracted with DCM (3×50 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under

reduced pressure to afford the title compound, which was used directly into next step without purification. MS: 546 (M+1).

Step 3: 5-chloro-2-fluoro-3-((1-((2-(1-hydroxyethyl)-4-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile

To a stirred solution of 5-chloro-2-fluoro-3-((1-((2-(1-hydroxyethyl)-4-methoxy-6-methylpyrimidin-5-yl)methyl)-2-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,2-dihydropyridin-3-yl)oxy)benzonitrile (80 mg, 0.147 mmol) in ACN (0.5 mL) was added KI (73.1 mg, 0.440 mmol) and TMS-Cl (0.056 mL, 0.440 mmol). And the resulting mixture was stirred at 70 °C for 2 h, and then concentrated under reduced pressure. The residue was purified by reverse phase HPLC (ACN/water with 0.1% TFA as modifier) to give a racemic mixture of the title compound. MS: 532 (M+1). The racemic mixture was purified by chiral SFC(IC-H column, 25% IPA/CO₂ with 0.1% NH₄OH as modifier) to afford **Example 44 isomer B** (slower eluting) as the title compound. MS: 532 (M+1). ¹H NMR (400 MHz, DMSO-*d*₆): δ ppm 8.82 (s, 1 H), 7.83 - 7.90 (m, 1 H), 7.72 (dd, *J*=7.40, 2.38 Hz, 1 H), 6.72 - 7.02 (m, 1 H), 5.67 (br s, 1 H), 4.91 (s, 2 H), 4.41 - 4.51 (m, 1 H), 2.38 (s, 3 H), 1.33 (d, *J*=6.72 Hz, 3 H).

EXAMPLE 45



5-chloro-2-fluoro-3-((1-((2-(hydroxymethyl)-4-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile

Step 1: 5-chloro-2-fluoro-3-((1-((4-methoxy-6-methyl-2-vinylpyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile

To a stirred solution of 5-chloro-2-fluoro-3-((6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile, **AB10** (442 mg, 0.967 mmol), 5-(chloromethyl)-4-methoxy-6-methyl-2-vinylpyrimidine, **C24** (240 mg, 0.967 mmol) in DMF (8 mL) was added

K₂CO₃ (267 mg, 1.933 mmol) and lithium bromide (126 mg, 1.450 mmol). The resulting mixture was stirred at 15 °C for 1 h. TLC (50% EtOAc/P.E.) showed the reaction was complete. The reaction mixture was diluted with H₂O (10 mL) and extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica (10-50% EtOAc/P.E.) to give the title compound. MS: 528 (M+1).

Step 2: 5-chloro-2-fluoro-3-((1-((2-formyl-4-methoxy-6-methylpyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile

To a stirred solution of 5-chloro-2-fluoro-3-((1-((4-methoxy-6-methyl-2-vinylpyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile (270 mg, 0.512 mmol) in 1,4-dioxane (10 mL) and water (3 mL), was added 2,6-dimethylpyridine (110 mg, 1.023 mmol), osmium(VIII) oxide (6.50 mg, 0.026 mmol) and sodium periodate (328 mg, 1.535 mmol). The resulting mixture was stirred at 15 °C for 30 min. TLC (50% EtOAc/P.E.) showed the reaction was complete. The reaction mixture was quenched with saturated aqueous solution of Na₂SO₃ (15 mL) and extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford the title compound, which was used directly into the next step. MS: 529.9 (M+1).

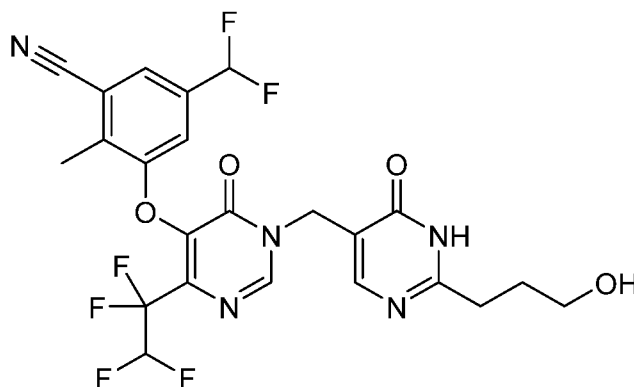
Step 3: 5-chloro-2-fluoro-3-((1-((2-(hydroxymethyl)-4-methoxy-6-methylpyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile

To a solution of 5-chloro-2-fluoro-3-((1-((2-formyl-4-methoxy-6-methylpyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile (80 mg, 0.151 mmol) in EtOAc (3 mL) was added 1M Zn(BH₄)₂ solution in DCM (0.151 mL, 0.151 mmol). The resulting mixture was stirred at 15°C for 3 min. TLC (66% EtOAc/P.E.) showed the completion of the reaction. The reaction mixture was quenched with H₂O (10 mL), extracted with EtOAc (3×10 mL). The combined the organic layers were dried over anhydrous Na₂SO₄, filtrated and concentrated under reduced pressure to obtain the title compound, which was used directly in the next step. MS: 532 (M+1).

Step 4: 5-chloro-2-fluoro-3-((1-((2-(hydroxymethyl)-4-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile

To a stirred solution of 5-chloro-2-fluoro-3-((1-((2-(hydroxymethyl)-4-methoxy-6-methylpyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile (70 mg, 0.132 mmol) in ACN (1.5 mL) was added KI (65.5 mg, 0.395 mmol) and TMS-Cl (0.050 mL, 0.395 mmol) under N₂ atmosphere. The resulting mixture was stirred at 70 °C for 2 h, and then purified directly by reverse phase HPLC (ACN/water with 0.1% TFA as modifier) to give the title compound. MS: 518 (M+1). ¹H NMR (400 MHz, DMSO-*d*₆): 8.81 (s, 1 H), 7.85 (dd, *J*=4.52, 2.54 Hz, 1 H), 7.71 (dd, *J*=7.28, 2.43 Hz, 1 H), 6.69 - 7.03 (m, 1 H), 4.92 (s, 2 H), 4.29 (s, 2 H), 2.38 (s, 3 H).

EXAMPLE 46



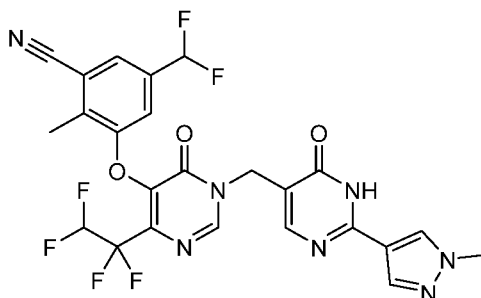
5-(difluoromethyl)-3-((1-((2-(3-hydroxypropyl)-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile
Step 1: 3-((1-((2-chloro-4-methoxypyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-5-(difluoromethyl)-2-methylbenzonitrile

To a solution of 5-(difluoromethyl)-2-methyl-3-((6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile, **AB07** (1 g, 2.65 mmol) in NMP (8.84 mL) was added K₂CO₃ (0.733 g, 5.30 mmol), and 2-chloro-5-(chloromethyl)-4-methoxypyrimidine, **C19** (0.537 g, 2.78 mmol). The resulting mixture was stirred at RT overnight. LC-MS analysis showed the desired product and no starting material. The reaction mixture was diluted with water, and stirred at RT for 30 minutes. The white precipitate was collected on top of a filter, and washed with water (3×), then air-dried to give the title compound. MS: 534.2 (M+1).

Step 2: 5-(difluoromethyl)-3-((1-((2-(3-hydroxypropyl)-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile

A mixture of 3-((1-((2-chloro-4-methoxypyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-5-(difluoromethyl)-2-methylbenzonitrile (30 mg, 0.056 mmol), potassium trifluoro(3-hydroxypropyl)borate (37.3 mg, 0.225 mmol), cesium carbonate (18.31 mg, 0.056 mmol), and chloro[(di(1-adamantyl)-*N*-butylphosphine)-2-(2-aminobiphenyl)]palladium(II)(cataCXimum A Pd G2 precatalyst (3.76 mg, 5.62 μ mol) was
 5 purged with N₂ and then added 1,4-dioxane (1.6 mL) and water (0.4 mL). The reaction mixture was heated at 120 °C in a microwave oven for 10 min. LC-MS showed desired product. The reaction mixture was diluted with Et₂O, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was retaken up with ACN(1.5 mL), and then treated with
 10 potassium iodide (28.0 mg, 0.169 mmol), and chlorotrimethylsilane (0.071 mL, 0.562 mmol). The resulting reaction mixture was heated at 100 °C for 10 min, then purified by reverse phase HPLC (ACN/water with 0.1% TFA as modifier) to afford the title compound. MS: 544.2 (M+1).

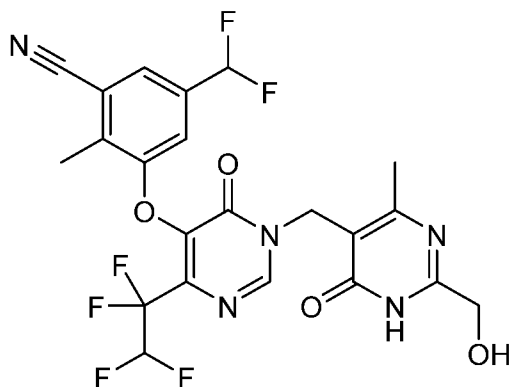
Example 47



5-(difluoromethyl)-2-methyl-3-((1-((2-(1-methyl-1*H*-pyrazol-4-yl)-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile

This compound was prepared in an analogous manner to that described in **Example 46** with (1-methyl-1*H*-pyrazol-4-yl)boronic acid. MS: 566.3 (M+1)

EXAMPLE 48



5-(difluoromethyl)-3-((1-((2-(hydroxymethyl)-4-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile

5 Step 1: 3-((1-((2-chloro-4-methoxy-6-methylpyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-5-(difluoromethyl)-2-methylbenzonitrile

To a stirred solution of 5-(difluoromethyl)-2-methyl-3-((6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile, **AB07** (1.5g, 3.98 mmol) and (2-chloro-4-methoxy-6-methylpyrimidin-5-yl)methanol, **C20** (0.750 g, 3.98 mmol) in toluene
 10 (30 mL) at 0 °C, was added triphenylphosphine (1.564 g, 5.96 mmol), and then DIAD (1.160 mL, 5.96 mmol) dropwise. The resulting reaction mixture was stirred at RT for 2 h, and then diluted with water (100 mL), extracted with EtOAc (3×80 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica(10-35% EtOAc/P.E.) to
 15 obtain the title compound. MS: 548.2 (M+1).

Step 2: 5-(difluoromethyl)-3-((1-((2-(hydroxymethyl)-4-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile

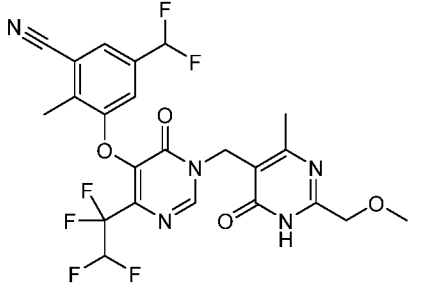
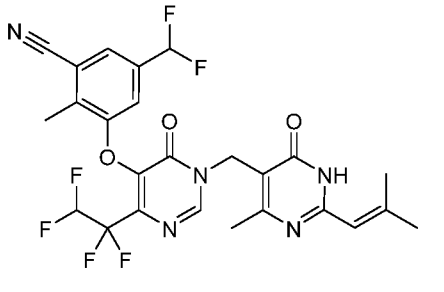
To a N₂ purged mixture of 3-((1-((2-chloro-4-methoxy-6-methylpyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-5-(difluoromethyl)-2-methylbenzonitrile (50 mg, 0.091 mmol), potassium trifluoro(((4-methoxybenzyl)oxy)methyl)borate (47.1 mg, 0.183 mmol) and cataCXium A Pd G2 precatalyst (12.20 mg, 0.018 mmol) in 1,4-dioxane (1 mL) and water (500 μL), was added 2M aqueous solution of cesium carbonate (500 μL, 1.000 mmol). The resulting reaction mixture was heated at 150 °C in a
 20

microwave oven for 10 min. LC-MS showed the desired product. The reaction mixture was extracted with Et₂O (2×). The combined organic layers were concentrated under reduced pressure. The residue was taken up by ACN (1 mL), and then treated with potassium iodide (45.5 mg, 0.274 mmol) and chlorotrimethylsilane (116 μL, 0.913 mmol). The mixture was heated at 100 °C for 10 min. LC-MS showed the desired product. The mixture was purified by reverse phase HPLC (ACN/water with 0.1% TFA as modifier) to afford the title compound. MS: 530.3 (M+1).

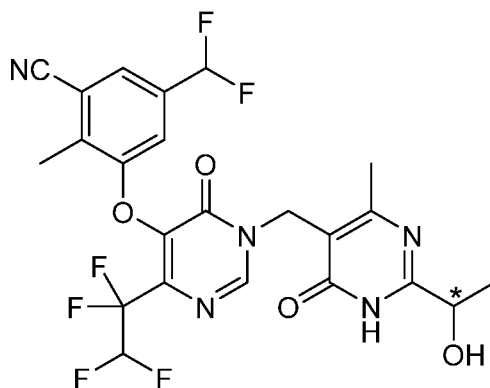
The following examples in Table 17 were prepared in an analogous manner to that described in **Example 48** with an appropriate intermediate AB and intermediate C using a corresponding boronic acid or potassium trifluoroborate for Step 2.

TABLE 17

Ex# (AB#, C#)	Structure	IUPAC Name	MS (M+1)
49 (AB07, C20)		5-(difluoromethyl)-3-((1-((2-(3-hydroxypropyl)-4-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile	558.2
50 (AB11, C20)		4-((1-((2-(3-hydroxypropyl)-4-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-3,5-dimethylbenzonitrile	522.2

51 (AB07, C20)		5-(difluoromethyl)-3-((1-((2-(methoxymethyl)-4-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile	544.3
52 (AB07, C20)		5-(difluoromethyl)-2-methyl-3-((1-((4-methyl-2-(2-methylprop-1-en-1-yl)-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile	554.3

EXAMPLES 53 (isomer mixture) and 54 (isomer A)



5-(difluoromethyl)-3-((1-((2-(1-hydroxyethyl)-4-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile (**53**, racemic mixture) and

5-(difluoromethyl)-3-((1-((2-(1-hydroxyethyl)-4-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile (**54**, single S or R isomer)

Step 1: 5-(difluoromethyl)-3-((1-((4-methoxy-6-methyl-2-vinylpyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile

A mixture of 3-((1-((2-chloro-4-methoxy-6-methylpyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-5-(difluoromethyl)-2-methylbenzonitrile (title compound from step 1 of **Example 48**) (230 mg, 0.420 mmol), potassium vinyltrifluoroborate (169 mg, 1.259 mmol), PdCl₂(dppf) (92 mg, 0.126 mmol) and cesium carbonate (850 mg, 2.61 mmol) in 1,4-dioxane (1679 μ L) and water (420 μ L) was purged with N₂, and heated at 150 °C in a microwave oven for 15 min. LC-MS showed the desired product as the major peak. The reaction mixture was partitioned between water and EtOAc (2 $\times$). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified with column chromatography on silica (40-100% EtOAc/hexanes) to afford the title compound. MS: 540.2 (M+1).

Step 2: 5-(difluoromethyl)-3-((1-((2-formyl-4-methoxy-6-methylpyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile

To a 20 mL of vial was added 5-(difluoromethyl)-3-((1-((4-methoxy-6-methyl-2-vinylpyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile (118 mg, 0.219 mmol), osmium tetroxide (274 μ L, 0.022 mmol), 2,6-dimethylpyridine (51.0 μ L, 0.437 mmol), and sodium periodate (140 mg, 0.656 mmol) in 1,4-dioxane (1641 μ L) and water (547 μ L). The resulting reaction mixture was stirred at RT for 48 h. The reaction solution was diluted with EtOAc (50 mL), then washed with saturated aqueous solution of NH₄Cl (2 $\times$ 20 mL), water (20 mL), brine (20 mL), then dried over anhydrous MgSO₄ and filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica (0-100 % EtOAc/hexanes) to afford the title compound. MS: 542.2 (M+1).

Step 3: 5-(difluoromethyl)-3-((1-((2-(1-hydroxyethyl)-4-methoxy-6-methylpyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-ethylbenzonitrile

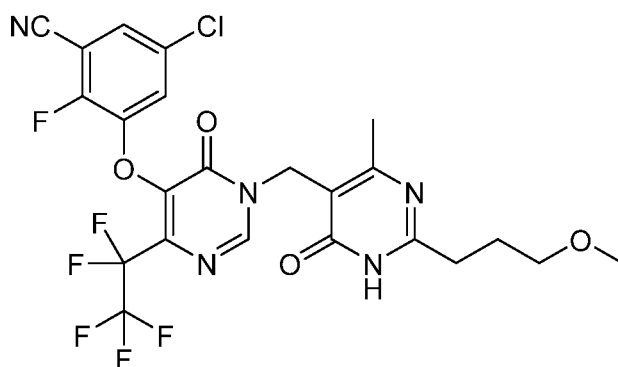
To a chilled (-78 °C) solution of 5-(difluoromethyl)-3-((1-((2-formyl-4-methoxy-6-methylpyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile (38 mg, 0.070 mmol) in THF (351 μ L) was added 3M solution of

methylmagnesium bromide in Et₂O (28.1 μ l, 0.084 mmol) dropwise. The resulting mixture was stirred at -78C till LC-MS showed complete consumption of the starting material. The reaction mixture was diluted with water, then extracted with EtOAc(2 $\times$). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give the title compound, which was used as is for the following step without further purification. MS: 558.3 (M+1).

Step 4: 5-(difluoromethyl)-3-((1-((2-(1-hydroxyethyl)-4-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile

To a mixture of 5-(difluoromethyl)-3-((1-((2-(1-hydroxyethyl)-4-methoxy-6-methylpyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile (34 mg, 0.061 mmol) in ACN(2 mL), was added KI (10 mg, 0.060 mmol) and TMS-Cl (66 μ L, 0.516 mmol). The resulting mixture was heated at 100 $^{\circ}$ C for 10 min in a microwave oven. LC-MS showed reaction was complete. The reaction mixture was diluted with water, then filtered and purified by reverse phase HPLC (CN/water with 0.1% TFA as modifier) to afford the title compound, **Example 53** (racemic mixture) MS: 544.2 (M+1). This racemic mixture was purified by chiral SFC (AD-H column, 15% MeOH/CO₂ with 0.1% DEA as modifier) to afford the title compound, **Example 54 isomer A** (faster eluting isomer). MS: 544.4 (M+1). ¹H NMR (600 MHz, Acetone-*d*₆) δ 8.77 (s, 1H), 7.64 (s, 1H), 7.21 (s, 1H), 6.80 (t, *J* = 48 Hz, 1H), 5.02 (s, 2H), 2.56 (s, 3H), 2.43 (s, 3H), 1.44 (d, *J* = 6.7 Hz, 3H).

EXAMPLE 55



5-chloro-2-fluoro-3-((1-((2-(3-methoxypropyl)-4-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile

Step 1: 5-chloro-3-((1-((2-chloro-4-methoxy-6-methylpyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-fluorobenzonitrile

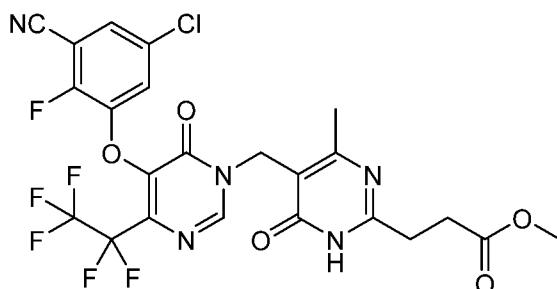
To a stirred solution of 5-chloro-2-fluoro-3-((6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile, **AB12** (0.73 g, 1.903 mmol) and 2-chloro-5-(chloromethyl)-4-methoxy-6-methylpyrimidine, **C20** (0.433 g, 2.093 mmol) in NMP (9.51 mL) was added K₂CO₃ (0.526 g, 3.81 mmol). The resulting mixture was stirred at RT overnight. LC-MS showed desired product. The reaction mixture was diluted with water (20 mL) and extracted with EtOAc (10 mL). The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The resulting mixture was purified by column chromatography on silica (0-100% EtOAc/hexanes) to provide the title compound. MS: 554.1 (M+1).

Step : 5-chloro-2-fluoro-3-((1-((2-(3-methoxypropyl)-4-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile

Degassed DME (474 µL) was added to a vial containing 5-chloro-3-((1-((2-chloro-4-methoxy-6-methylpyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-fluorobenzonitrile (35 mg, 0.063 mmol), tris(trimethylsilyl)silane (21.43 µL, 0.069 mmol), [4,4'-bis(1,1-dimethylethyl)-2,2'-bipyridine-*N*1,*N*1']bis[3,5-difluoro-2-[5-(trifluoromethyl)-2-pyridinyl-*N*]phenyl-C]Iridium(III) hexafluorophosphate, (Ir[dF(CF₃)ppy]₂(dtbpy))PF₆ (0.708 mg, 0.632 µmol), 1-bromo-3-methoxypropane (6.00 mg, 0.063 mmol) and anhydrous Na₂CO₃ (13.39 mg, 0.126 mmol). The resulting vial was placed under N₂ and 250 µL of the nickel stock solution [prepared by sonicating a mixture of NiCl₂DME (35 mg) and 4,4'-di-tert-butyl-2,2'-dipyridyl (40 mg) in degassed DME (10 mL) under N₂ for 10 min]. The resulting mixture was sealed and irradiated with a 34 W Kessil® LED lamp (7 cm away, with cooling fan to keep the temperature at 25 °C) overnight. The reaction was quenched by exposure to air. The reaction mixture was diluted with water (2 mL) and EtOAc (2 mL). The organic layer was separated and concentrated under reduced pressure. The resulting crude was dissolved in DMF (1 mL) and pyridine hydrochloride (36.2 mg) was added. The resulting mixture was stirred at 120 °C for 30 min. The reaction was diluted with DMSO (1mL) and purified by reverse phase HPLC (ACN/water with 0.1% TFA as modifier) to afford the title compound. MS: 578.2 (M+1). ¹H NMR (600 MHz, DMSO-*d*₆): δ 8.81 (d, J = 5.6

Hz, 1H), 7.85 (m, 1H), 7.81 (m, 1H), 4.92 (s, 2H), 4.43 (t, J = 6.1 Hz, 1H), 3.42 (t, J = 6.1 Hz, 1H), 2.63 (t, J = 7.4 Hz, 1H), 2.57 (t, J = 7.4 Hz, 1H), 2.36 (s, 3H), 2.35 (s, 3H), 2.08 (m, 1H), 1.78 (m, 1H).

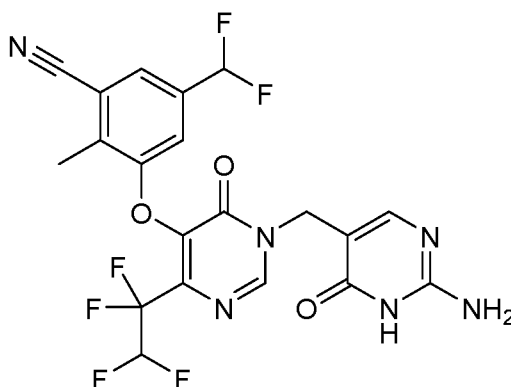
EXAMPLE 56



Methyl 3-((5-((5-chloro-3-cyano-2-fluorophenoxy)-6-oxo-4-(perfluoroethyl)pyrimidin-1(6H)-yl)methyl)-4-methyl-6-oxo-1,6-dihydropyrimidin-2-yl)propanoate

This compound was prepared in an analogous manner to that described in **Example 56** with methyl 3-bromopropanoate. MS: 592.2 (M+1).

EXAMPLE 57



3-((1-((2-amino-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-5-(difluoromethyl)-2-methylbenzonitrile

Step 1: 3-((1-((2-chloro-4-methoxypyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-5-(difluoromethyl)-2-methylbenzonitrile

To a chilled (0 °C) suspension of 5-(difluoromethyl)-2-methyl-3-((6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydro pyrimidin-5-yl)oxy)benzonitrile, **AB07** (1.4 g, 3.71 mmol) and K₂CO₃ (0.513 g, 3.71 mmol) in DMF (18.56 mL), was added 2-chloro-5-(chloromethyl)-4-methoxypyrimidine, **C19** (0.860 g, 4.45 mmol). The resulting suspension was stirred at RT for

10 min. when LC-MS showed completion of reaction. The reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography on silica (0-80 % EtOAc/hexanes) to afford the title compound. MS: 534.1 (M+1).

Step 2: 5-(difluoromethyl)-3-((1-((4-methoxy-2-((4-methoxybenzyl)amino)pyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile

To a solution of 3-((1-((2-chloro-4-methoxypyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-5-(difluoromethyl)-2-methylbenzonitrile (95 mg, 0.178 mmol) in THF (890 μ L) was added 4-methoxybenzylamine (48.8 mg, 0.356 mmol). The resulting reaction mixture was stirred at 60 °C overnight. LC-MS indicates the reaction was complete. The reaction mixture was concentrated under reduced pressure. The residue was taken up in EtOAc (10 mL), washed with saturated aqueous NaHCO₃ solution, and dried over anhydrous MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica (0-100 % EtOAc/hexanes) to afford the title compound. MS: 635.2 (M+1).

Step 3: 3-((1-((2-amino-4-methoxypyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-5-(difluoromethyl)-2-methylbenzonitrile

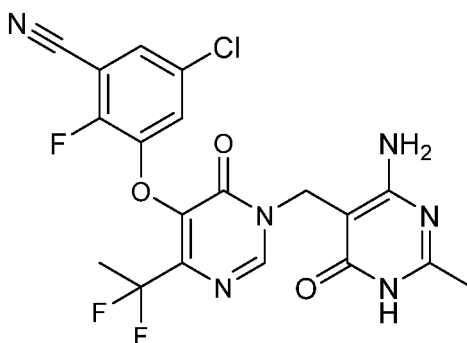
To a solution of 5-(difluoromethyl)-3-((1-((4-methoxy-2-((4-methoxybenzyl)amino)pyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile 0389804-0171 (110 mg, 0.173 mmol) in DCM (867 μ L), was added TFA (134 μ L, 1.734 mmol) and TFAA (24.49 μ L, 0.173 mmol). The resulting reaction mixture was heated to 100 °C for 1 h. LC-MS indicates reaction was complete. The mixture was concentrated under reduced pressure to give the title compound, which was used directly in the following step with purification. MS: 515.2 (M+1).

Step 4: 3-((1-((2-amino-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-5-(difluoromethyl)-2-methylbenzonitrile

To a solution of 3-((1-((2-amino-4-methoxypyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-5-(difluoromethyl)-2-methylbenzonitrile (85 mg, 0.165 mmol) in ACN (826 μ L) was added TMS-I (225 μ L, 1.652 mmol). The resulting reaction mixture was heated to 110 °C in a microwave oven till LC-MS showed the reaction was

at completion. The reaction solution was diluted with EtOAc (10 mL), and washed with saturated aqueous Na₂SO₃, filtered and purified by reverse phase HPLC (ACN/water with 0.1% TFA as modifier) to afford the title compound. MS: 501.2 (M+1).

EXAMPLE 58



3-((1-((4-amino-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-4-(1,1-difluoroethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-5-chloro-2-fluorobenzonitrile

Step 1: 5-chloro-3-((1-((4-chloro-6-methoxy-2-methylpyrimidin-5-yl)methyl)-4-(1,1-difluoroethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-2-fluorobenzonitrile

To a solution of 5-chloro-3-((4-(1,1-difluoroethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-2-fluorobenzonitrile, **AB34** (100 mg, 0.303 mmol) in DMF (3 mL) were added 4-chloro-5-(chloromethyl)-6-methoxy-2-methylpyrimidine, **C22** (69.1 mg, 0.334 mmol), potassium carbonate (126 mg, 0.910 mmol) and lithium bromide (26.3 mg, 0.303 mmol). The resulting mixture was stirred at 25 °C for 8 h, and then concentrated under reduced pressure. The residue was purified by preparative TLC plates (50% EtOAc/P.E.) to give the title compound. MS: 500.1 (M+1)

Step 2: 5-chloro-3-((9-(1,1-difluoroethyl)-4-methoxy-11-(4-methoxybenzyl)-2-methyl-7-oxo-7,10,10a,11-tetrahydro-5H-dipyrimido[1,2-a:4',5'-d]pyrimidin-8-yl)oxy)-2-fluorobenzonitrile

To a solution of 5-chloro-3-((1-((4-chloro-6-methoxy-2-methylpyrimidin-5-yl)methyl)-4-(1,1-difluoroethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-2-fluorobenzonitrile (60 mg, 0.120 mmol) and (4-methoxyphenyl)methanamine (16.45 mg, 0.120 mmol) in DMA (2 mL) was added TEA (0.033 mL, 0.240 mmol). The resulting mixture was stirred at 80°C for 4 h, and then concentrated under reduced pressure. The residue was purified by column chromatography on silica (0-20% EtOAc/P.E.) to afford the title compound. MS: 601.(2M+1).

Step 3: 3-((1-((4-amino-6-methoxy-2-methylpyrimidin-5-yl)methyl)-4-(1,1-difluoroethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-5-chloro-2-fluorobenzonitrile

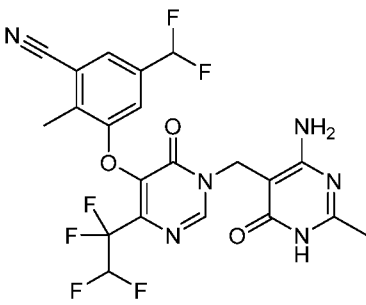
To a solution of 5-chloro-3-((4-(1,1-difluoroethyl)-1-((4-methoxy-6-((4-methoxybenzyl)amino)-2-methylpyrimidin-5-yl)methyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-2-fluorobenzonitrile (30 mg, 0.050 mmol) in TFA (3 mL) was added TFAA (7.05 μ L, 0.050 mmol). The resulting reaction solution was stirred at 80 °C for 0.5 h, and then concentrated under reduced pressure to afford the title compound. MS: 481.1 (M+1).

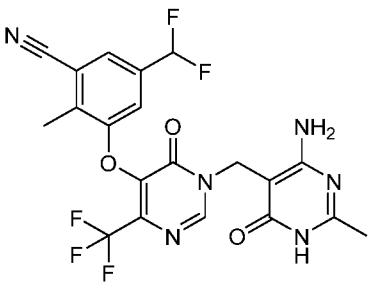
Step 4: 3-((1-((4-amino-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-4-(1,1-difluoroethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-5-chloro-2-fluorobenzonitrile

To a solution of 3-((1-((4-amino-6-methoxy-2-methylpyrimidin-5-yl)methyl)-4-(1,1-difluoroethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-5-chloro-2-fluorobenzonitrile (15 mg, 0.031 mmol) in ACN (3 mL) were added KI (15.54 mg, 0.094 mmol) and TMS-Cl (0.012 mL, 0.094 mmol). The resulting mixture was stirred at 70 °C for 2 h. LC-MS showed the reaction was complete. The reaction mixture was concentrated under reduced pressure. The residue was purified by reverse phase HPLC (ACN/water with 0.1% TFA as modifier) to afford the title compound. MS: 481.1 (M+1). ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.72 (br s, 1 H) 8.58 (s, 1 H) 7.79 - 7.89 (m, 1 H) 7.66 (dd, *J*=7.34, 2.32 Hz, 1 H) 6.65 (br s, 2 H) 4.78 (s, 2 H) 2.15 (s, 3 H) 1.93 (t, *J*=19.44 Hz, 3 H).

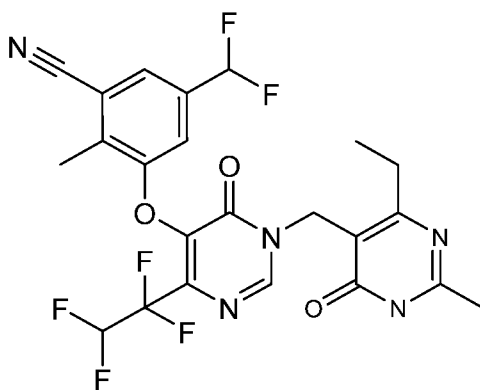
The following examples in Table 18 were prepared in an analogous manner to that described in **Example 58** with a corresponding intermediate AB.

TABLE 18

Ex# (AB#)	Structure	IUPAC Name	MS (M+1)
59 (AB07)		3-((1-((4-amino-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-5-(difluoromethyl)-2-methylbenzonitrile	515.2

60 (AB05)		3-((1-((4-amino-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(trifluoromethyl)-1,6-dihydropyrimidin-5-yl)oxy)-5-(difluoromethyl)-2-methylbenzonitrile	483.2
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EXAMPLE 61



5-(difluoromethyl)-3-((1-((4-ethyl-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile

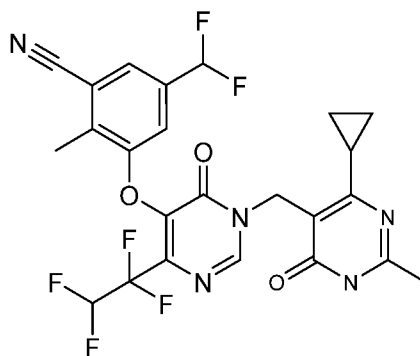
Step 1: 3-((1-((4-chloro-6-methoxy-2-methylpyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-5-(difluoromethyl)-2-methylbenzonitrile

To a solution of 5-(difluoromethyl)-2-methyl-3-((6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile, **AB07** (392 mg, 1.039 mmol) and 4-chloro-5-(chloromethyl)-6-methoxy-2-methylpyrimidine, **C22** (323 mg, 1.56 mmol) in DMF (3464 μ L) was added K_2CO_3 (287 mg, 2.078 mmol). The resulting reaction mixture was stirred at RT overnight. LC-MS showed the reaction was complete. The reaction mixture was diluted with water, and then extracted with EtOAc (3 $\times$). The combined organic layers were concentrated under reduced pressure. The residue was purified with column chromatography on silica (0-100% EtOAc/hexanes) to afford the title compound. MS: 548.2 (M+1).

Step 2: 5-(difluoromethyl)-3-((1-((4-ethyl-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile

A mixture of 3-((1-((4-chloro-6-methoxy-2-methylpyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-5-(difluoromethyl)-2-methylbenzonitrile (10.9 mg, 0.020 mmol), ethylboronic acid (21 mg, 0.284 mmol), Cs₂CO₃ (19.45 mg, 0.060 mmol), and cataCXium A Pd G2 precatalyst (5.32 mg, 7.96 μmol) was flushed with N₂, then treated with 1,4-dioxane (500 μL) and water (50 μL). The resulting mixture was heated at 150 °C in a microwave oven for 10 min. LC-MS showed the reaction was complete. The reaction mixture was extracted with Et₂O (2×). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was taken up in ACN (1 mL), and KI (9.91 mg, 0.060 mmol) and TMS-Cl (25.4 μL, 0.199 mmol) was added. The resulting mixture was heated at 100 °C for 2 h. The reaction mixture was filtered and purified with reverse phase HPLC (ACN/water with 0.1% TFA as modifier) to afford the title compound. MS: 528.2 (M+1).

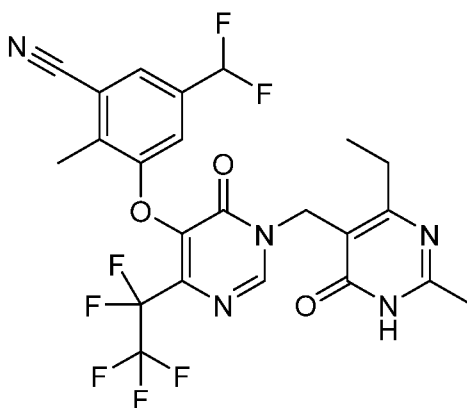
Example 62



2-((1-((4-cyclopropyl-6-methoxy-2-methylpyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-5-(difluoromethyl)-2-methylbenzonitrile

This compound was prepared in an analogous manner to that described in **Example 61** with cyclopropylboronic acid. MS: 540.2 (M+1)

EXAMPLE 63



5-(difluoromethyl)-3-((1-((4-ethyl-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile

Step 1: 3-((1-((4-chloro-6-methoxy-2-methylpyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-5-difluoromethyl)-2-methylbenzonitrile

To a solution of 5-(difluoromethyl)-2-methyl-3-((6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile, **AB06** (1200 mg, 3.04 mmol) and 4-chloro-5-(chloromethyl)-6-methoxy-2-methylpyrimidine, **C22** (711 mg, 3.43 mmol) in DMF (15.2 mL) was added K₂CO₃ (839 mg, 6.07 mmol). The resulting reaction mixture was stirred at RT overnight. LC-MS indicated the reaction was complete. The reaction mixture was poured into EtOAc (20 mL) and washed with water (2×10 mL) and brine. The organic layer was dried over anhydrous MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica (0-75% EtOAc/hexanes) to afford the title compound. MS: 566.0 (M+1).

Step 2: 5-(difluoromethyl)-3-((1-((4-ethyl-6-methoxy-2-methylpyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile

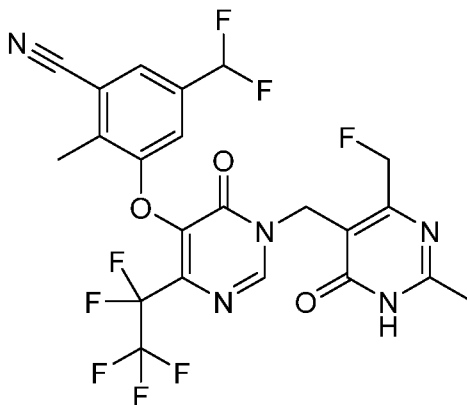
A mixture of 3-((1-((4-chloro-6-methoxy-2-methylpyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-5-difluoromethyl)-2-methylbenzonitrile (50 mg, 0.088 mmol), ethylboronic acid (9.79 mg, 0.133 mmol), chloro[(di(1-adamantyl)-n-butylphosphine)-2-(2-aminobiphenyl)]palladium(II) (5.91 mg, 8.84 μmol) and Cs₂CO₃ (86 mg, 0.265 mmol) was purged with N₂, then dissolved in water (80 μL) and 1,4-dioxane (803 μL). The resulting mixture was heated to 100 °C for 16 h, and then filtered over CELITE[®]. The

filtrate was diluted with EtOAc (10 mL), and washed with water (2×3 mL). The organic layer was dried over anhydrous MgSO₄ and concentrated under reduced pressure. The residue was purified on column chromatography on silica (0-100 % EtOAc/hexanes) to afford the title compound. MS: 560.1 (M+1).

5 Step 3: 5-(difluoromethyl)-3-((1-((4-ethyl-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile

To a solution of 5-(difluoromethyl)-3-((1-((4-ethyl-6-methoxy-2-methylpyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile (18 mg, 0.032 mmol) in DMF (1000 μL) was added pyridine hydrochloride (18.59 mg, 0.161 mmol). The resulting mixture was heated to 120 °C for 15 min. LC-MS showed the reaction was complete. The reaction mixture was diluted with DMSO (1 mL) and purified by reverse phase HPLC (ACN/water with 0.1% TFA modifier) to afford the title compound. MS: 546.1 (M+1)

EXAMPLE 64



15 5-(difluoromethyl)-3-((1-((4-(difluoromethyl)-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile

Step 1: 3-((1-((4-chloro-6-methoxy-2-methylpyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-5-(difluoromethyl)-2-methylbenzonitrile

20 To a solution of 5-(difluoromethyl)-2-methyl-3-((6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile, **AB06** (1750 mg, 4.43 mmol) and 4-chloro-5-(chloromethyl)-6-methoxy-2-methylpyrimidine, **C22** (1 g, 4.83 mmol) in DMF (22.14 mL) was added K₂CO₃ (1.224 g, 8.86 mmol). The resulting reaction mixture was stirred at RT for 16 h.

The solution was poured into EtOAc (20 mL) and washed with water (2×10 mL) and brine. The organic layer was dried over anhydrous MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica (0-75% EtOAc:hexanes) to afford title compound. MS: 566.1 (M+1).

5 Step 2: 5-(difluoromethyl)-3-((1-((4-methoxy-6-(((4-methoxybenzyl)oxy)methyl)-2-methylpyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile

3-((1-((4-chloro-6-methoxy-2-methylpyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-5-(difluoromethyl)-2-methylbenzonitrile (150 mg, 0.265 mmol) was dissolved in water (241 µL) and 1,4-dioxane (2410 µL) and degassed. And then
10 CataCXium A Pd G2 precatalyst (17.73 mg, 0.027 mmol), potassium trifluoro(((4-methoxybenzyl)oxy)methyl)borate (103 mg, 0.398 mmol) and Cs₂CO₃ (259 mg, 0.795 mmol) were added to the reaction. The resulting reaction mixture was degassed and heated to 100 °C for 1 h, and then filtered and concentrated under reduced pressure. The residue was purified by column
15 chromatography on silica (0-100% EtOAc/hexanes) to afford title compound. MS: 682.1 (M+1).

Step 3: 5-(difluoromethyl)-3-((1-((4-(hydroxymethyl)-6-methoxy-2-methylpyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile

To a solution of 5-(difluoromethyl)-3-((1-((4-methoxy-6-(((4-methoxybenzyl)oxy)methyl)-2-methylpyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile (123 mg, 0.180 mmol) in CH₂Cl₂ (1805 µl), was added TFA
20 (139 µL, 1.805 mmol). The resulting reaction mixture was stirred at RT for 16 h. The material was concentrated under reduced pressure to isolate the title compound. MS: 562.1 (M+1).

Step :4 5-(difluoromethyl)-3-((1-((4-(fluoromethyl)-6-methoxy-2-methylpyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile

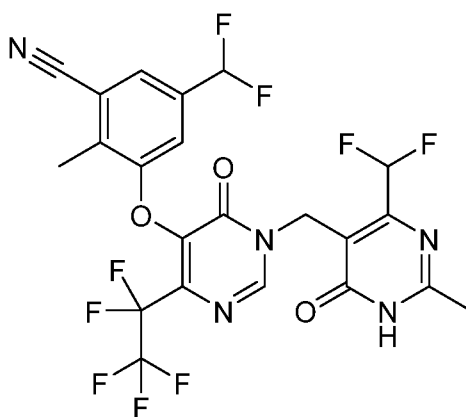
25 A solution of 5-(difluoromethyl)-3-((1-((4-(hydroxymethyl)-6-methoxy-2-methylpyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile (101 mg, 0.180 mmol) in DCM (900 µl) was treated with DAST (59.4 µL, 0.450 mmol) and stirred at 55 °C for 72 h. The solution was diluted with DCM (10 mL) and quenched slowly with saturated aqueous NaHCO₃ solution until pH ~7. The organic layer was

then dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to isolate the title compound. MS: 564.1 (M+1).

Step 5: 5-(difluoromethyl)-3-((1-((4-(fluoromethyl)-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile

5 A solution of 5-(difluoromethyl)-3-((1-((4-(fluoromethyl)-6-methoxy-2-methylpyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile (100 mg, 0.177 mmol) in DMF (1775 µL) was treated with pyridine hydrochloride (103 mg, 0.887 mmol). The resulting reaction mixture was heated to 120 °C in a microwave oven for 15 min. The reaction mixture was filtered and purified by reverse phase HPLC (ACN/water with
10 0.05% NH₄OH as modifier) to isolate the title compound. MS: 550.1 (M+1). ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.78 (s, 1H), 7.73 (s, 1H), 7.25 (s, 1H), 6.86 (t, J = 55.3 Hz, 1H), 5.38 (d, J = 46.8 Hz, 2H), 4.96 (s, 2H), 2.43 (s, 3H), 2.27 (s, 3H).

EXAMPLE 65



15 5-(difluoromethyl)-3-((1-((4-(difluoromethyl)-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile
Step 1: 5-(difluoromethyl)-3-((1-((6-methoxy-2-methyl-4-vinyl-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile

A mixture of 3-((1-((4-chloro-6-methoxy-2-methylpyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-5-(difluoromethyl)-2-methylbenzonitrile, the
20 title compound from Step 1 of **Example 63**) (200 mg, 0.353 mmol), tributyl(vinyl)stannane (208 µL, 0.707 mmol), and bis(triphenylphosphone)palladium(II) dichloride (49.6 mg, 0.071 mmol) in toluene (3535 µL) was stirred at 100 °C for 16 h. The mixture was partitioned between

EtOAc and saturated KF solution. The resulting solution was stirred for 30 min then filtered and the organic layer was separated and concentrated under reduced pressure. The residue was purified by column chromatography on silica (0-80% EtOAc/hexanes) to afford the title compound. MS: 558.1 (M+1).

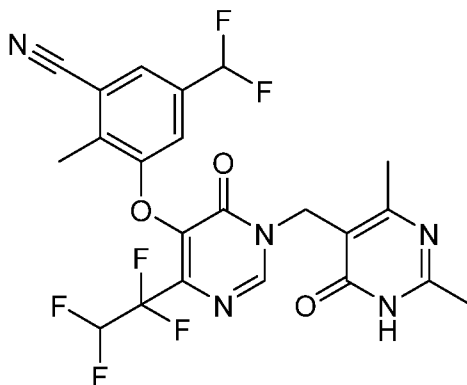
5 Step 2: 5-(difluoromethyl)-3-((1-((4-formyl-6-methoxy-2-methylpyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile

To a solution of 5-(difluoromethyl)-3-((1-((6-methoxy-2-methyl-4-vinyl-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile (100 mg, 0.179 mmol) in dioxane (1345 μ L):water (448 μ L), was added
 10 2.5% (by weight) solution of osmium(VIII) oxide in t-butanol (225 μ L, 0.018 mmol), 2,6-dimethylpyridine (41.6 μ L, 0.359 mmol), and sodium periodate (115 mg, 0.538 mmol). The resulting reaction mixture was stirred at 25 °C for 24 h. The mixture was diluted with EtOAc (50 mL) and washed with saturated aqueous NH₄Cl (2×20 mL), water (20 mL), brine (20 mL), dried over anhydrous MgSO₄ and concentrated under reduced pressure. The residue was purified
 15 by column chromatography on silica (0-60% EtOAc/hexanes) to afford the title compound. MS: 560.1 (M+1).

Step 3: 5-(difluoromethyl)-3-((1-((4-(difluoromethyl)-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile

A solution of 5-(difluoromethyl)-3-((1-((4-formyl-6-methoxy-2-methylpyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile (40
 20 mg, 0.072 mmol) in DCM (358 μ L) was treated with DAST (23.62 μ L, 0.179 mmol). The resulting reaction solution was stirred at RT for 2 h, and then concentrated under reduced pressure. The residue was taken up with f DMF (1 mL), treated with pyridine hydrochloride (83 mg, 0.715 mmol), and heated to 120 °C for 15 min increments until all starting material was
 25 consumed. The reaction mixture was filtered and purified by reverse phase HPLC (ACN/water with 0.1% TFA as modifier) to afford the title compound. MS: 568.1 (M+1). ¹H NMR (500 MHz, DMSO-*d*₆) δ 12.98 (s, 1H), 8.80 (s, 1H), 7.75 (s, 1H), 7.48 – 6.65 (m, 3H), 5.05 (s, 2H), 2.49 (p, J = 1.8 Hz, 3H), 2.31 (s, 3H).

EXAMPLE 66



5-(difluoromethyl)-3-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile

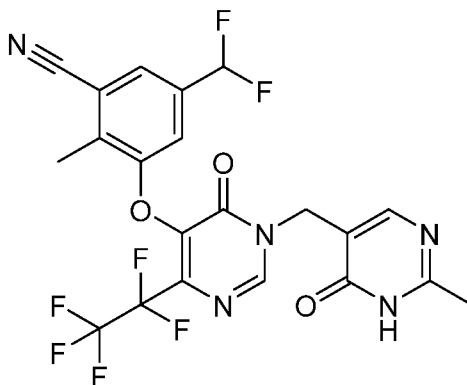
Step 1: 5-(difluoromethyl)-3-((1-((4-methoxy-2,6-dimethylpyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile

A mixture of 5-fluoro-3-((4-methoxy-2,6-dimethylpyrimidin-5-yl)methyl)-6-(1,1,2,2-tetrafluoroethyl)pyrimidin-4(3H)-one, **BC05** (23 mg, 0.063 mmol), 5-(difluoromethyl)-3-hydroxy-2-methylbenzonitrile, **A02** (11.56 mg, 0.063 mmol), and potassium carbonate (26.2 mg, 0.189 mmol) in NMP (210 μ L) was heated at 80°C till LC-MS showed complete conversion. The reaction mixture was diluted with water, and the precipitate was collected on top of a filter and washed with water(3 $\times$), then air-dried to afford the title compound. MS: 528.2 (M+1).

Step 2: 5-(difluoromethyl)-3-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile

A mixture of 5-(difluoromethyl)-3-((1-((4-methoxy-2,6-dimethylpyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile and potassium iodide (10.48 mg, 0.063 mmol) in ACN (2 mL) was treated with TMS-Cl (48.4 μ L, 0.379 mmol), then heated at 100 °C for 10 minutes. The reaction mixture was filtered and purified with reverse phase HPLC (ACN/water with 0.1% TFA as modifier) to afford the title compound. MS: 514.2 (M+1). ^1H NMR (600 MHz, CDCl_3) δ 8.65 (s, 1H), 7.44 (s, 1H), 6.73 (s, 1H), 4.99 (s, 2H), 2.59 (s, 3H), 2.55 (s, 3H), 2.49 (s, 3H).

EXAMPLE 67



5-(difluoromethyl)-2-methyl-3-((1-((2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile

Step 1: 5-(difluoromethyl)-3-((1-((4-methoxy-2-methylpyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile

A mixture of 5-fluoro-3-((4-methoxy-2-methylpyrimidin-5-yl)methyl)-6-(perfluoroethyl)pyrimidin-4(3H)-one, **BC02** (16 mg, 0.043 mmol), 5-(difluoromethyl)-3-hydroxy-2-methylbenzonitrile, **A02** (7.96 mg, 0.043 mmol), and potassium carbonate (18.02 mg, 0.130 mmol) in NMP (145 μ L) was heated at 80 $^{\circ}$ C for 1 h. The reaction mixture was diluted with water and the precipitate was collected on top of a filter and washed with water (2 $\times$), and air-dried to obtain the title compound, which was used as is for the next step. MS: 532.2 (M+1).

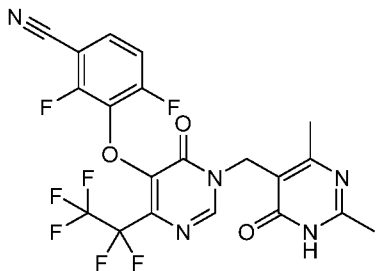
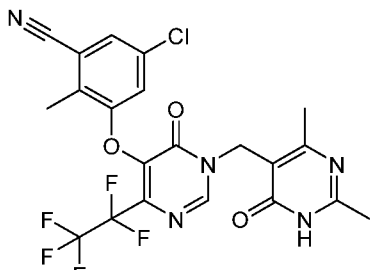
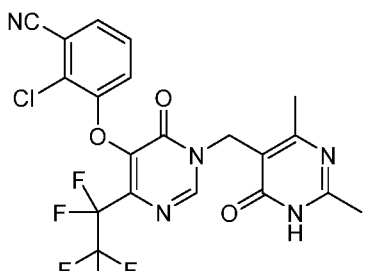
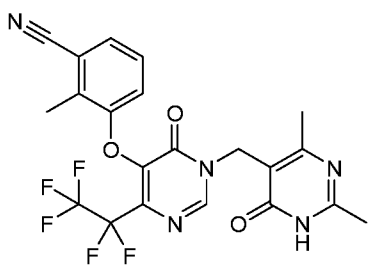
Step 2: 5-(difluoromethyl)-2-methyl-3-((1-((2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile

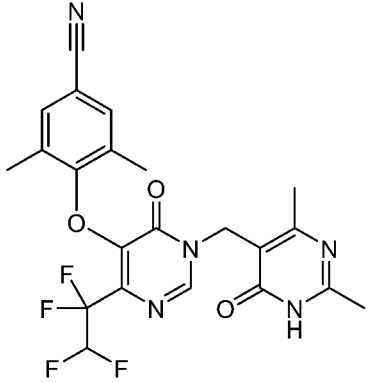
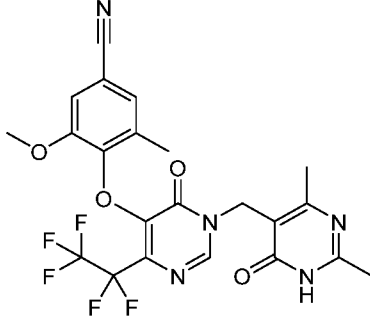
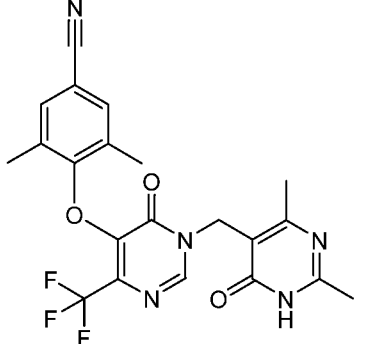
The above crude material and KI (21.64 mg, 0.130 mmol) in ACN (2 mL) was treated with TMS-Cl (70 μ L, 0.548 mmol), then heated to 100 $^{\circ}$ C till LC-MS showed the reaction was complete. The reaction mixture was purified by reverse phase HPLC (ACN/water with 0.1% TFA as modifier) to afford the title compound. MS: 518.2 (M+1). ^{1} H NMR (600 MHz, Methanol- d_4) δ 8.67 (s, 2H), 8.04 (s, 2H), 7.60 (s, 2H), 7.03 (s, 2H), 6.68 (s, 1H), 3.30 (s, 19H), 2.54 (s, 6H), 2.45 (s, 6H), 1.93 (s, 1H).

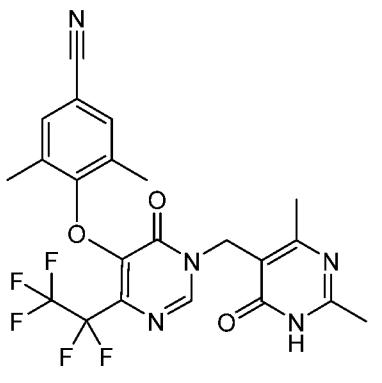
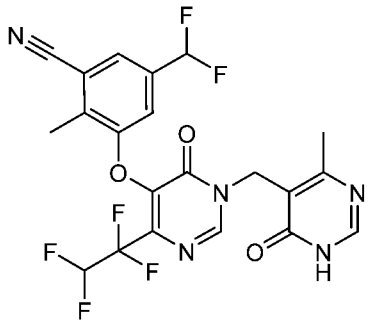
The following examples in Table 19 were prepared in an analogous manner to that described in **Example 67** with an appropriate intermediate BC and intermediate A.

TABLE 19

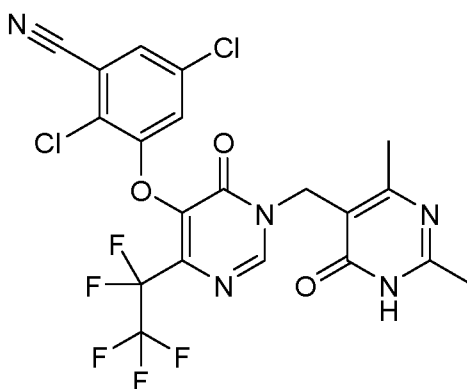
Ex# (BC#, A#)	Structure	IUPAC Name	MS (M+1)
68 (BC05, A10)		2-chloro-3-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-5-methylbenzonitrile	498.0
69 (BC05, A01)		3-(difluoromethyl)-5-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile	500.1
70 (BC03, A02)		5-(difluoromethyl)-2-methyl-3-((1-((2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile	500.2

71 (BC0, A17)		3-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2,4-difluorobenzonitrile	504.2
72 (BC01, A07)		5-chloro-3-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile	516.2
73 (BC01, A18)		3-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile	502.1
74 (BC01, A19)		3-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile	482.2

75 (BC05, A20)		4-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-3,5-dimethylbenzonitrile	477
76 (BC01, A21)		4-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-3-methoxy-5-methylbenzonitrile	512.3
77 (BC04, A20)		4-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(trifluoromethyl)-1,6-dihydropyrimidin-5-yl)oxy)-3,5-dimethylbenzonitrile	446.2

78 (BC01, A20)		4-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-3,5-dimethylbenzonitrile	496.2
79 (BC06, A02)		5-(difluoromethyl)-2-methyl-3-((1-((4-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile	500.2

EXAMPLE 80



5 2,5-dichloro-3-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile
Step 1: 2,5-dichloro-3-((1-((4-methoxy-2,6-dimethylpyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile

To a solution of 5-(difluoromethyl)-2-methyl-3-((6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile, **BC01** (200 mg, 0.523 mmol) in ACN (2616 μ L), was added potassium carbonate (72.3 mg, 0.523 mmol) and 2,5-dichloro-3-hydroxybenzonitrile, **A04** (118 mg, 0.628 mmol). The reaction mixture was stirred at 100 °C for 16 h, and then filtered.

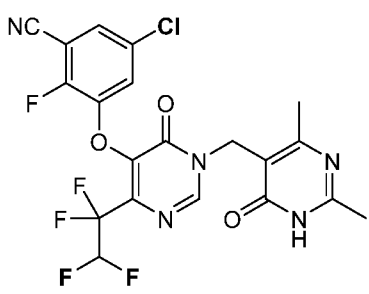
The filtrate was diluted with EtOAc (200 mL) and hexanes (20 mL), and washed with water (3 $\times$ 50 mL), brine (50 mL), dried over anhydrous MgSO₄, filtered and concentrated under reduced pressure. The residue was purified with column chromatography on silica (0-70% EtOAc/hexanes) to afford the title compound. MS: 550.2 (M+1).

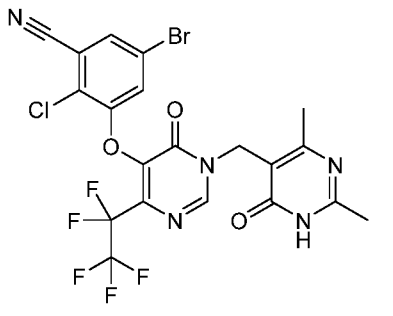
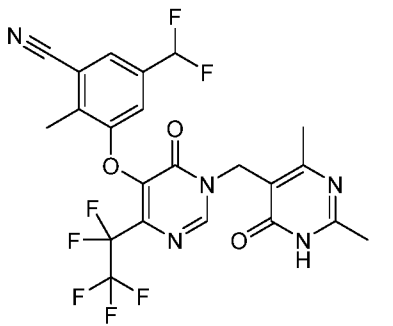
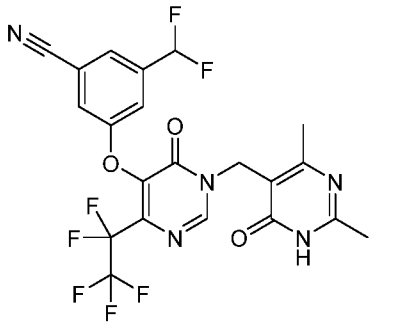
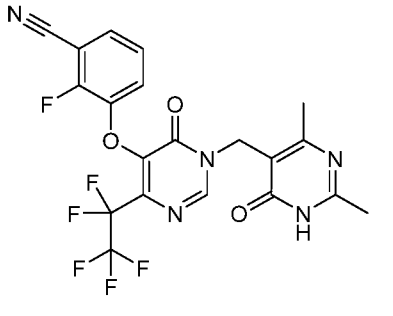
Step 2: 2,5-dichloro-3-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile

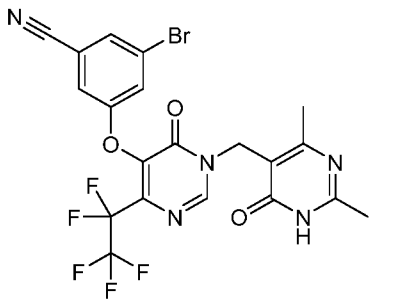
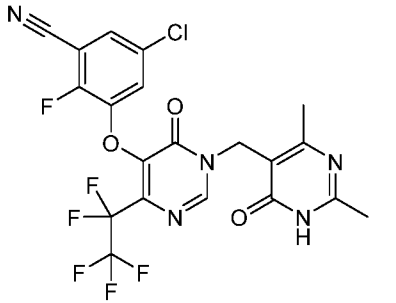
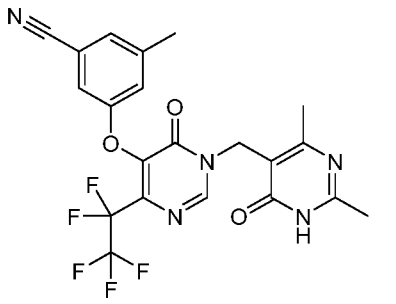
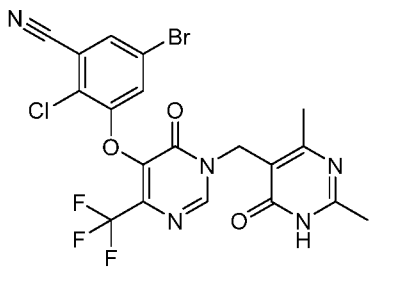
To a solution of 2,5-dichloro-3-((1-((4-methoxy-2,6-dimethylpyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile (154 mg, 0.280 mmol) in ACN (2799 μ L) was added TMS-I (381 μ L, 2.80 mmol). The resulting reaction mixture was stirred at RT for 2 days. LC-MS showed complete conversion. The reaction is quenched with saturated aqueous Na₂SO₃ (300 μ L) and purified by reverse phase HPLC (ACN/water with 0.05% NH₄OH as modifier) to afford the title compound. MS: 536.1 (M+1). ¹H NMR (600 MHz, DMSO-*d*₆) δ 8.79 (s, 1H), 7.92 (d, *J* = 2.1 Hz, 1H), 7.73 (d, *J* = 2.1 Hz, 1H), 4.89 (s, 2H), 2.31 (s, 3H), 2.22 (s, 3H).

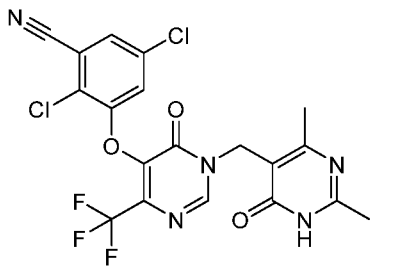
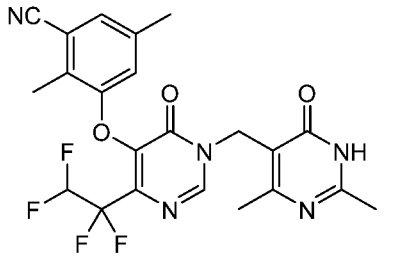
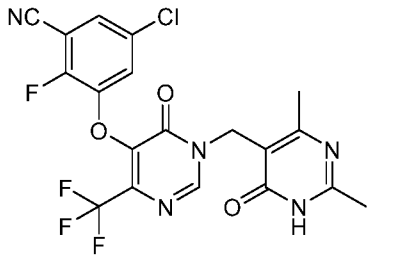
The following examples in Table 20 were prepared in an analogous manner to that described in **Example 80** with appropriate intermediate BC and intermediate A.

TABLE 20

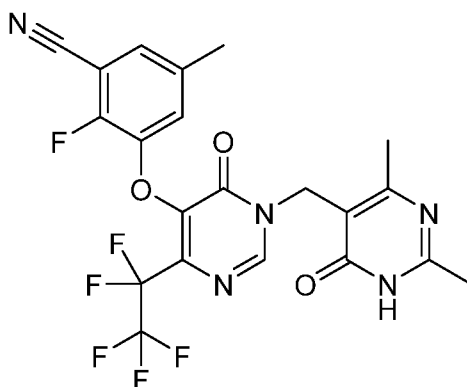
Ex# (BC#, A#)	Structure	IUPAC Name	MS (M+1)
81 (BC05, A06)		5-chloro-3-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-fluorobenzonitrile	502.1

82 (BC01, A03)		5-bromo-2-chloro-3-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile	580.1 and 582.1
83 (BC01, A02)		5-(difluoromethyl)-3-((1-((4-methoxy-2,6-dimethylpyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile	532.2
84 (BC01, A01)		3-(difluoromethyl)-5-((1-((4-methoxy-2,6-dimethylpyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile	518.2
85 (BC01, A11)		3-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-fluorobenzonitrile	486.1

86 (BC01, A12)		3-bromo-5-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile	546.1 and 548.1
87 (BC01, A06)		5-chloro-3-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-fluorobenzonitrile	520.2
88 (BC01, A13)		3-((1-((4-methoxy-2,6-dimethylpyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-5-methylbenzonitrile	482.1
89 (BC04, A03)		5-bromo-2-chloro-3-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(trifluoromethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile	530.1 and 532.1

90 (BC04, A04)		2,5-dichloro-3-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(trifluoromethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile	486.1
91 (BC05, A14)		3-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2,5-dimethylbenzonitrile	477.2
92 (BC04, A06)		5-chloro-3-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(trifluoromethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-fluorobenzonitrile	470.1

EXAMPLE 93



3-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-fluoro-5-methylbenzonitrile

Step 1: 5-chloro-2-fluoro-3-((1-((4-methoxy-2,6-dimethylpyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile

To a solution of 5-fluoro-3-((4-methoxy-2,6-dimethylpyrimidin-5-yl)methyl)-6-(perfluoroethyl)pyrimidin-4(3H)-one, **BC01** (115 mg, 0.301 mmol) in ACN (1504 μ L) was added potassium carbonate (83 mg, 0.602 mmol) and 5-chloro-2-fluoro-3-hydroxybenzonitrile, **A05** (61.9 mg, 0.361 mmol). The resulting reaction mixture was stirred at r.t. for 16 h, and then filtered. The filtrate was diluted with EtOAc (200 mL) and hexanes (20 mL), then washed with water (3 $\times$ 50 mL), brine (50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified with column chromatography on silica (0-70% EtOAc/hexanes) to afford the title compound. MS: 534.2 (M+1).

Step 2: 5-methyl-2-fluoro-3-((1-((4-methoxy-2,6-dimethylpyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile

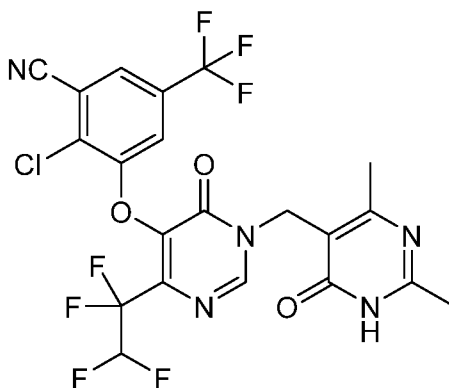
To a degassed mixture of 5-chloro-2-fluoro-3-((1-((4-methoxy-2,6-dimethylpyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile (90 mg, 0.169 mmol) in water (211 μ L) and 1,4-dioxane (632 μ L), was added chloro[(di(1-adamantyl)-n-butylphosphine)-2-(2-aminobiphenyl)]palladium(II) (11.27 mg, 0.017 mmol), potassium methyltrifluoroborate (30.8 mg, 0.253 mmol) and Cs_2CO_3 (165 mg, 0.506 mmol). The resulting reaction mixture was heated to 130 $^{\circ}C$ for 30 minutes. LC-MS showed that the reaction was complete. The reaction mixture was concentrated under reduced pressure. The residue was purified on column chromatography on silica (0-80% EtOAc/hexanes) to afford the title compound. MS: 514.2 (M+1).

Step 3: 3-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-fluoro-5-methylbenzonitrile

A solution of 3-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-fluoro-5-methylbenzonitrile (32 mg, 0.062 mmol) was dissolved in ACN (312 μ L) was treated with TMS-I (42.4 μ L, 0.312 mmol). The resulting reaction mixture was heated to 40 $^{\circ}C$ for 4 h. LC-MS showed the reaction was complete. The reaction was quenched with saturated aqueous Na_2SO_3 (100 μ L) and stirred for 30 minutes. DMSO (2 mL) was added to the solution was purified by reverse phase HPLC (ACN/water with 0.05% NH_4OH as modifier) to afford the title compound. MS: 500.2 (M+1).

^1H NMR (600 MHz, DMSO- d_6) δ 8.76 (s, 1H), 7.41 (d, J = 3.9 Hz, 1H), 7.32 (d, J = 7.5 Hz, 1H), 5.05 (s, 2H), 2.30 (s, 3H), 2.22 (s, 3H), 2.21 (s, 3H).

EXAMPLE 94



2-chloro-3-(((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-5-(trifluoromethyl)benzonitrile

Step 1: 5-(3-bromo-2-chloro-5-(trifluoromethyl)phenoxy)-3-((4-methoxy-2,6-dimethylpyrimidin-5-yl)methyl)-6-(1,1,2,2-tetrafluoroethyl)pyrimidin-4(3H)-one

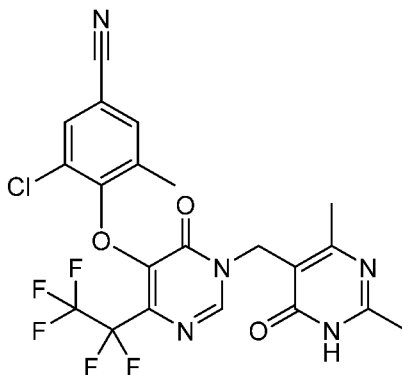
To a stirred solution of 5-fluoro-3-((4-methoxy-2,6-dimethylpyrimidin-5-yl)methyl)-6-(1,1,2,2-tetrafluoroethyl)pyrimidin-4(3H)-one, **BC05** (50 mg, 0.137 mmol) and 3-bromo-2-chloro-5-(trifluoromethyl)phenol (41.6 mg, 0.151 mmol) in DMF (1 mL) was added K_2CO_3 (37.9 mg, 0.275 mmol) at RT. The resulting mixture was stirred at 120°C overnight. LC-MS showed desired product. The reaction mixture was diluted with water (5 mL) and extracted with EtOAc (5 mL). The organic layer was concentrated under reduced pressure. The residue was purified by column chromatography on silica (0-100% EtOAc/hexanes) to afford the title compound. MS: 621.0 (M+1).

Step 2: 2-chloro-3-(((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-5-(trifluoromethyl)benzonitrile

A mixture of 5-(3-bromo-2-chloro-5-(trifluoromethyl)phenoxy)-3-((4-methoxy-2,6-dimethylpyrimidin-5-yl)methyl)-6-(1,1,2,2-tetrafluoroethyl)pyrimidin-4(3H)-one (37 mg, 0.060 mmol), $\text{Zn}(\text{CN})_2$ (4.21 mg, 0.036 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (6.90 mg, 5.97 μmol) in DMF (600 μL) was degassed for 5 min and then heated at 120 °C overnight. LC-MS showed desired product. The reaction mixture was diluted with DMF (1 mL), and then filtered and treated with pyridine hydrochloride (20.70 mg, 0.179 mmol). The resulting mixture was stirred at 120 °C for

20 min. LC-MS showed the final product. The residue was purified by reverse phase HPLC (ACN/water with 0.1% TFA as modifier) to afford the title compound. MS: 552.1 (M+1). ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.81 (s, 1H), 8.23 (s, 1H), 7.78 (s, 1H), 3.84 (s, 2H), 2.32 (s, 3H), 2.27 (s, 3H).

EXAMPLE 95



3-chloro-4-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-5-methylbenzonitrile

Step 1: 5-(2-chloro-4-methoxy-6-methylphenoxy)-3-((4-methoxy-2,6-dimethylpyrimidin-5-yl)methyl)-6-(perfluoroethyl)pyrimidin-4(3H)-one

To a vial was added 2-chloro-4-methoxy-6-methylphenol (45.2 mg, 0.262 mmol), 5-fluoro-3-((4-methoxy-2,6-dimethylpyrimidin-5-yl)methyl)-6-(perfluoroethyl)pyrimidin-(3H)-one, **BC01** (100 mg, 0.26 mmol), potassium carbonate (90 mg, 0.65 mmol) and DMF (2.6 mL). The resulting reaction mixture was heated to 100 °C for 15 h, cooled to ambient temperature and then filtered through a syringe filter. The crude solution was purified by reverse phase HPLC (ACN/water with 0.1% TFA as modifier) to afford the title compound. MS: 535.3 (M+1).

Step 2: 5-(2-chloro-4-hydroxy-6-methylphenoxy)-3-((4-methoxy-2,6-dimethylpyrimidin-5-yl)methyl)-6-(perfluoroethyl)pyrimidin-4(3H)-one

To a ice-cooled solution of 5-(2-chloro-4-methoxy-6-methylphenoxy)-3-((4-methoxy-2,6-dimethylpyrimidin-5-yl)methyl)-6-(perfluoroethyl)pyrimidin-4(3H)-one (87 mg, 0.16 mmol) in DCM (3 mL) was added 1M solution of BBr₃ in DCM(0.34 mL, 0.34 mmol) dropwise. The resulting reaction mixture was allowed to warm to ambient temperature, stirred for 15 h, and then quenched by the addition of methanol (2 mL). The resulting mixture was concentrated

under reduced pressure. The residue was purified by column chromatography on silica (0-100% EtOAc/ hexanes, and then 10% MeOH/DCM) to afford the title compound. MS: 521.2 (M+1).

Step 3: 3-chloro-4-((1-((4-methoxy-2,6-dimethylpyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-5-methylphenyl trifluoromethanesulfonate

To a solution of 5-(2-chloro-4-hydroxy-6-methylphenoxy)-3-((4-methoxy-2,6-dimethylpyrimidin-5-yl)methyl)-6-(perfluoroethyl)pyrimidin-4(3H)-one (100 mg, 0.19 mmol) in DCM (3 mL) was added triethylamine (0.04 mL, 0.29 mmol) and N,N-bis(trifluoromethyl sulfonyl)aniline (82 mg, 0.23 mmol). The resulting reaction mixture was allowed to stir at ambient temperature for 2 h and then quenched by the addition of saturated aqueous sodium bicarbonate (10 mL). The reaction mixture was extracted by DCM (3×10 mL). The combined organic layers were dried over anhydrous MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica (0-100% EtOAc/hexanes) to afford the title compound. MS: 653.2 (M+1).

Step 4: 3-chloro-4-((1-((4-methoxy-2,6-dimethylpyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-5-methylbenzonitrile

A mixture of 3-chloro-4-((1-((4-methoxy-2,6-dimethylpyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-5-methylphenyl trifluoromethanesulfonate (62 mg, 0.10 mmol), tbuXPhos Pd G3 precatalyst (30.2 mg, 0.038 mmol), and zinc cyanide (7.36 mg, 0.063 mmol) was purged with nitrogen three times before water (1.5 mL) and THF (0.38 mL) were added. The resulting reaction mixture was heated to 65 °C for 15 h, cooled to ambient temperature, filtered over a pad of CELITE[®] and concentrated under reduced pressure. The residue was purified by column chromatography on silica (0-100% EtOAc/hexanes) to afford the title compound. MS: 530.2 (M+1).

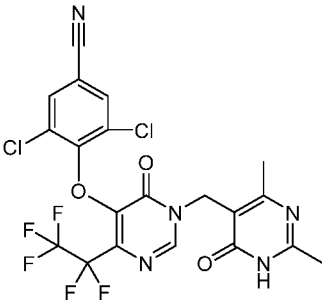
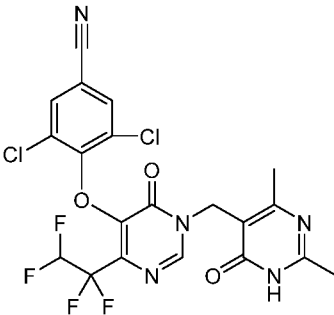
Step 5: 3-chloro-4-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-5-methylbenzonitrile

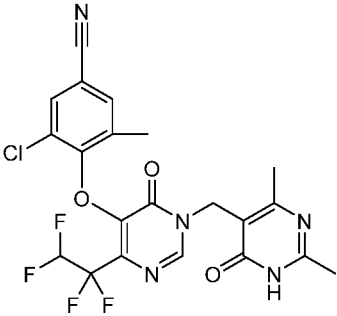
To a stirred solution of 3-chloro-4-((1-((4-methoxy-2,6-dimethylpyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-5-methylbenzonitrile (16 mg, 0.030 mmol) and potassium iodide (15.04 mg, 0.091 mmol) in ACN (302 µL), was added TMS-Cl (11.58 µl, 0.091 mmol). The resulting mixture was heated to 50°C overnight. LC-MS showed complete and clean conversion. The reaction mixture was cooled, and quenched with MeOH (1

mL), and concentrated under reduced pressure. The residue was purified by reverse phase HPLC (ACN/water with 0.1% TFA as modifier) to give fractions containing desired product, which were combined, diluted with saturated aqueous NaHCO₃ solution, and extracted with DCM (3×). The combined organic layers were dried over anhydrous MgSO₄, filtered and concentrated under reduced pressure to afford the title compound. MS: 516.2 (M+1). ¹H NMR (500 MHz, CDCl₃): δ 8.5 (s, 1H), 7.4 (s, 2H), 5.0 – 4.8 (dd, 2H), 2.55 (s, 3H), 2.5 (s, 3H), 2.3 (s, 3H).

The following examples in Table 21 were prepared in an analogous manner to that described in **Example 95** with appropriate intermediate BC and intermediate A.

TABLE 21

Ex# (BC#, A#)	Structure	IUPAC Name	MS (M+1)
96 (BC01, A15)		3,5-dichloro-4-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile	536.2
97 (BC05, A15)		3,5-dichloro-4-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile	518.2

98 (BC05, A16)		3-chloro-4-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-5-methylbenzonitrile	498.2
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Determination of cell kill (HIV-TACK) activity:

PBMCs derived from healthy donors were grown in complete media (RPMI 1640 with L-glutamine; 10% heat inactivated Fetal Bovine Serum; 100 U/mL Penicillin-Streptomycin) containing 5 µg/mL Phytohemagglutinin at about 2.5×10^6 cells/mL for 3 days at 5% CO₂, 37°C, and 90% humidity. On day 4, PHA stimulated cells were washed and resuspended at about 20×10^6 cells/mL in complete media with IL-2 (10 U/mL) with VSV-G pseudotyped HIV virus stock (VSV-G/pNLG1-P2A-ΔEnv - 20 µg/mL p24) and incubated for 4 hours at 37°C, 5% CO₂ and 90% humidity. VSV-G/pNLG1-P2A-ΔEnv is a VSV-G pseudotyped virus derived from pNL43 with *egfp* inserted 5' of *nef* and eGFP expression driven off normal spliced RNA transcripts.

Virus contained Vif truncated by 50 amino acids due to deletion of a single nucleotide causing a frameshift and does not express Nef due to a stop codon after *gfp*. HIV Env is not expressed due to a frameshift resulting in multiple stop codons. Infected cells were then washed with complete media plus 10U/mL IL-2 3-times with centrifuging at 200 x g for 3 minutes at 22°C. Cells were resuspended at 5×10^6 cells/mL in complete media plus 10 U/mL IL-2 and incubated overnight at 37°C, 5% CO₂ and 90% humidity. For compound treatment infected PBMCs were diluted to 4×10^5 cells/mL with RPMI 1640 with L-glutamine, 50% Normal Human Serum (NHS), 100 U/mL Penicillin-Streptomycin plus IL-2 (10 U/mL) and 20,000 cells were transferred to each well in a 384-well poly-D-lysine coated compound plate containing compounds with final DMSO <0.5%. Compounds were tested with 10-point 3-fold titration. Plates were analyzed on an Acumen ex3 imager using the Blue Laser 488 nm and the number of GFP positive objects were collected with loss of GFP representing death of infected cells. Titration curves and EC₅₀ values were calculated using a four-parameter logistic fit. Results are shown in Table 22.

TABLE 22

Ex. No.	TACK EC ₅₀ (nM)	Ex. No.	TACK EC ₅₀ (nM)	Ex. No.	TACK EC ₅₀ (nM)	Ex. No.	TACK EC ₅₀ (nM)
1	431.0	26	413.0	51	394.8	76	498.0
2	411.4	27	450.7	52	456.0	77	409.4
3	416.9	28	208.4	53	391.5	78	155.9
4	411.5	29	312.0	54	212.9	79	459.8

Ex. No.	TACK EC50 (nM)	Ex. No.	TACK EC50 (nM)	Ex. No.	TACK EC50 (nM)	Ex. No.	TACK EC50 (nM)
5	186.8	30	205.7	55	276.0	80	340.0
6	201.2	31	396.8	56	161.4	81	156.3
7	353.3	32	170.8	57	493.3	82	530.9
8	251.7	33	208.1	58	252.1	83	251.8
9	287.0	34	474.0	59	134.6	84	291.0
10	146.2	35	350.8	60	227.9	85	440.7
11	267.0	36	72.3	61	485.2	86	472.8
12	199.5	37	114.1	62	406.3	87	217.5
13	395.0	38	480.6	63	276.5	88	397.1
14	343.0	39	265.1	64	162.0	89	433.7
15	244.7	40	198.4	65	382.3	90	489.1
16	199.4	41	363.1	66	262.5	91	325.3
17	282.4	42	307.8	67	174.4	92	283.6
18	128.6	43	437.7	68	477.9	93	172.0
19	315.3	44	333.3	69	340.5	94	491.9
20	364.9	45	257.2	70	202.6	95	179.2
21	131.8	46	303.3	71	148.6	96	366.6
22	181.0	47	393.9	72	377.2	97	182.4
23	428.7	48	341.8	73	450.0	98	183.0
24	338.8	49	277.8	74	483.8		
25	353.2	50	249.6	75	208.6		

WHAT IS CLAIMED IS:

1. A compound selected from the group consisting of:

5-(difluoromethyl)-2-methoxy-3-((1-((2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile;
3-(difluoromethyl)-5-((1-((2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile;
2,5-dichloro-3-((4-(1,1-difluoroethyl)-1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile;
5-chloro-3-((4-(1,1-difluoroethyl)-1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile;
5-(difluoromethyl)-3-((1-((2,6-dimethyl-4-oxo-4,5-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2-trifluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile;
3-((4-(1,1-difluoroethyl)-1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-5-(difluoromethyl)-2-methylbenzonitrile;
3-bromo-5-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile;
5-(difluoromethyl)-3-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(trifluoromethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile;
3-((4-(1,1-difluoroethyl)-1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-5-(difluoromethyl)-2-methoxybenzonitrile;
5-(difluoromethyl)-3-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-methoxybenzonitrile;
4-((4-(1,1-difluoroethyl)-1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-3,5-dimethylbenzonitrile;

3-chloro-4-((4-(1,1-difluoroethyl)-1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-5-methylbenzonitrile;
3,5-dichloro-4-((4-(1,1-difluoroethyl)-1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile;
3-((4-(1,1-difluoroethyl)-1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-2,4,5-trifluorobenzonitrile;
3-((4-(1,1-difluoroethyl)-1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-5-(difluoromethyl)-2-fluorobenzonitrile;
4-((4-(1,1-difluoroethyl)-1-((4-hydroxy-2,6-dimethylpyrimidin-5-yl)methyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-3-methyl-5-(trifluoromethyl)benzonitrile;
3-cyclopropyl-4-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-5-methylbenzonitrile;
3-(difluoromethyl)-4-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-5-methylbenzonitrile;
2-chloro-5-(difluoromethyl)-3-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile;
5-(difluoromethyl)-3-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-4-(1-fluoroethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile;
3-((4-(1,1-difluoroethyl)-1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-5-(difluoromethyl)benzonitrile;
5-chloro-3-((4-(1,1-difluoroethyl)-1-((4-methyl-6-oxo-2-((pyrimidin-2-yloxy)methyl)-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-2-fluorobenzonitrile;
3-((4-(1,1-difluoroethyl)-1-((4-methyl-6-oxo-2-((pyrimidin-2-yloxy)methyl)-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-5-(difluoromethyl)-2-methylbenzonitrile;

3-((4-bromo-1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-2,5-dimethylbenzonitrile;
2-amino-5-chloro-3-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile;
<i>S</i> -5-(difluoromethyl)-3-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-4-(1-fluoroethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile;
(<i>R</i>)-5-(difluoromethyl)-3-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-4-(1-fluoroethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile;
(<i>S</i>)-5-chloro-3-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-4-(1-fluoroethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-2-fluorobenzonitrile;
(<i>R</i>)-5-chloro-3-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-4-(1-fluoroethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-2-fluorobenzonitrile;
(<i>S</i>)-5-(difluoromethyl)-3-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-4-(1-fluoroethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-2-fluorobenzonitrile;
(<i>R</i>)-5-(difluoromethyl)-3-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-4-(1-fluoroethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-2-fluorobenzonitrile ;
(<i>S</i>)-5-(difluoromethyl)-3-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-4-(1-fluoroethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-2-methoxybenzonitrile;
(<i>R</i>)-5-(difluoromethyl)-3-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-4-(1-fluoroethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-2-methoxybenzonitrile;
3-((1-((4-amino-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-5-(difluoromethyl)-2-methylbenzonitrile;
3-((1-((4-amino-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-5-chloro-2-fluorobenzonitrile;
3-((1-((4-amino-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-5-chloro-2-fluorobenzonitrile;

3-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-fluoro-5-methylbenzonitrile;
3-((4-(1,1-difluoroethyl)-1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-2-fluoro-5-methylbenzonitrile;
3-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-5-ethyl-2-fluorobenzonitrile;
5-chloro-2-fluoro-3-((1-((2-(hydroxymethyl)-4-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile;
5-(difluoromethyl)-3-((1-((2-(3-hydroxypropyl)-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile;
5-(difluoromethyl)-2-methyl-3-((1-((2-(1-methyl-1 <i>H</i> -pyrazol-4-yl)-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile;
5-(difluoromethyl)-3-((1-((2-(hydroxymethyl)-4-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile;
5-(difluoromethyl)-3-((1-((2-(3-hydroxypropyl)-4-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile;
4-((1-((2-(3-hydroxypropyl)-4-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-3,5-dimethylbenzonitrile;
5-(difluoromethyl)-3-((1-((2-(methoxymethyl)-4-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile;

5-(difluoromethyl)-2-methyl-3-((1-((4-methyl-2-(2-methylprop-1-en-1-yl)-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile;
5-chloro-2-fluoro-3-((1-((2-(3-methoxypropyl)-4-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile;
Methyl 3-(5-((5-(5-chloro-3-cyano-2-fluorophenoxy)-6-oxo-4-(perfluoroethyl)pyrimidin-1(6H)-yl)methyl)-4-methyl-6-oxo-1,6-dihydropyrimidin-2-yl)propanoate;
3-((1-((2-amino-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-5-(difluoromethyl)-2-methylbenzonitrile;
3-((1-((4-amino-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-4-(1,1-difluoroethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-5-chloro-2-fluorobenzonitrile;
3-((1-((4-amino-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-5-(difluoromethyl)-2-methylbenzonitrile;
3-((1-((4-amino-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(trifluoromethyl)-1,6-dihydropyrimidin-5-yl)oxy)-5-(difluoromethyl)-2-methylbenzonitrile;
5-(difluoromethyl)-3-((1-((4-ethyl-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile;
2-((1-((4-cyclopropyl-6-methoxy-2-methylpyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-5-(difluoromethyl)-2-methylbenzonitrile;
5-(difluoromethyl)-3-((1-((4-ethyl-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile;
5-(difluoromethyl)-3-((1-((4-(fluoromethyl)-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile;
5-(difluoromethyl)-3-((1-((4-(difluoromethyl)-2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile;

5-(difluoromethyl)-3-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile;
5-(difluoromethyl)-2-methyl-3-((1-((2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile;
2-chloro-3-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-5-methylbenzonitrile;
3-(difluoromethyl)-5-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile;
5-(difluoromethyl)-2-methyl-3-((1-((2-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile;
3-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2,4-difluorobenzonitrile;
5-chloro-3-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile;
3-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile;
3-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile;
4-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-3,5-dimethylbenzonitrile;
4-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-3-methoxy-5-methylbenzonitrile;
4-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(trifluoromethyl)-1,6-dihydropyrimidin-5-yl)oxy)-3,5-dimethylbenzonitrile;
4-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-3,5-dimethylbenzonitrile;

5-(difluoromethyl)-2-methyl-3-((1-((4-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile;
2,5-dichloro-3-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile;
5-chloro-3-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-fluorobenzonitrile;
5-bromo-2-chloro-3-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile;
5-(difluoromethyl)-3-((1-((4-methoxy-2,6-dimethylpyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile;
3-(difluoromethyl)-5-((1-((4-methoxy-2,6-dimethylpyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile;
3-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-fluorobenzonitrile;
3-bromo-5-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile;
5-chloro-3-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-fluorobenzonitrile;
3-((1-((4-methoxy-2,6-dimethylpyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-5-methylbenzonitrile;
5-bromo-2-chloro-3-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(trifluoromethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile;
2,5-dichloro-3-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(trifluoromethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile;
3-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2,5-dimethylbenzonitrile;

5-chloro-3-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(trifluoromethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-fluorobenzonitrile;
3-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-fluoro-5-methylbenzonitrile;
2-chloro-3-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-5-(trifluoromethyl)benzonitrile;
3-chloro-4-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-5-methylbenzonitrile;
3,5-dichloro-4-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(perfluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile;
3,5-dichloro-4-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile; and
3-chloro-4-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-5-methylbenzonitrile;

or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1 that is:

(3,5-dichloro-4-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-4-(1-fluoroethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile, and the (<i>S</i>) and (<i>R</i>) stereoisomers thereof;
(3-chloro-4-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-4-(1-fluoroethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-5-methylbenzonitrile, and the (<i>S</i>) and (<i>R</i>) stereoisomers thereof;
2,5-dichloro-3-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-4-(1-fluoroethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)benzonitrile, and the (<i>S</i>) and (<i>R</i>) stereoisomers thereof;

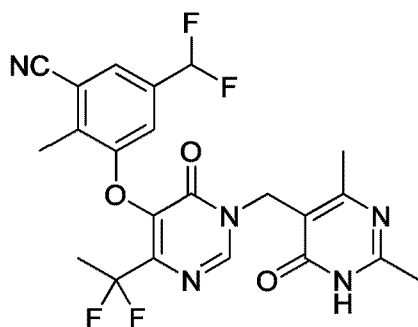
4-((1-((2,4-dimethyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-4-(1-fluoroethyl)-6-oxo-1,6-dihydropyrimidin-5-yl)oxy)-3,5-dimethylbenzonitrile, and the (*S*) and (*R*) stereoisomers thereof;

5-chloro-2-fluoro-3-((1-((2-(1-hydroxyethyl)-4-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-2-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,2-dihydropyridin-3-yl)oxy)benzonitrile, and the (*S*) and (*R*) stereoisomers thereof; or

5-(difluoromethyl)-3-((1-((2-(1-hydroxyethyl)-4-methyl-6-oxo-1,6-dihydropyrimidin-5-yl)methyl)-6-oxo-4-(1,1,2,2-tetrafluoroethyl)-1,6-dihydropyrimidin-5-yl)oxy)-2-methylbenzonitrile, and the (*S*) and (*R*) stereoisomers thereof;

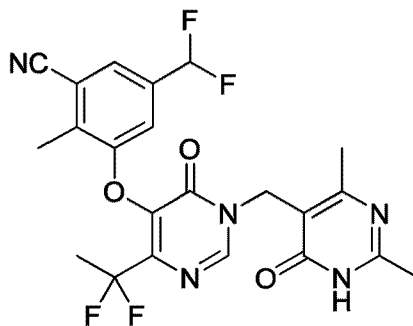
or a pharmaceutically acceptable salt thereof.

3. The compound of claim 1 that is

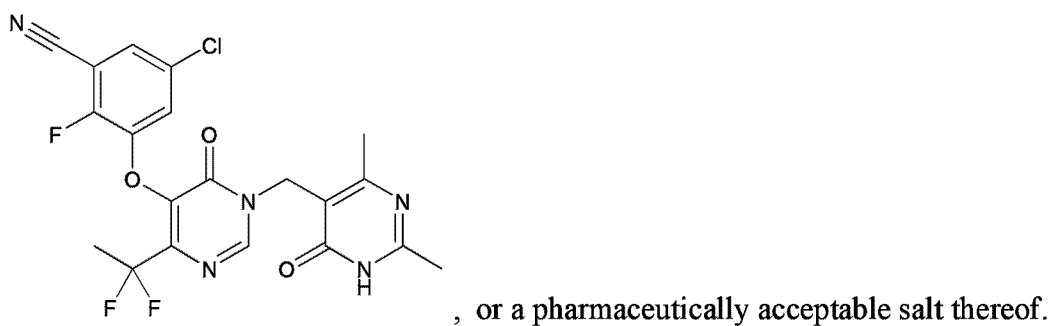


, or a pharmaceutically acceptable salt thereof.

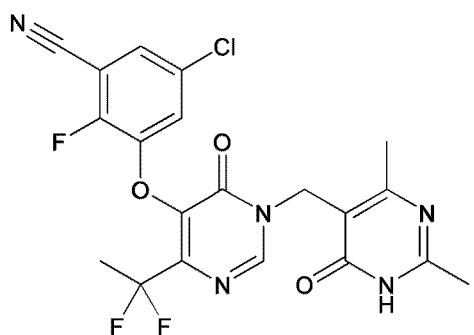
4. The compound of claim 3 that is



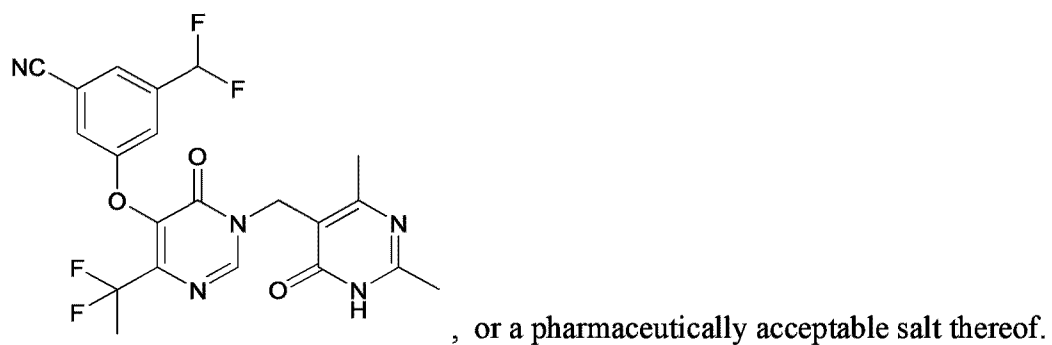
5. The compound of claim 1 that is



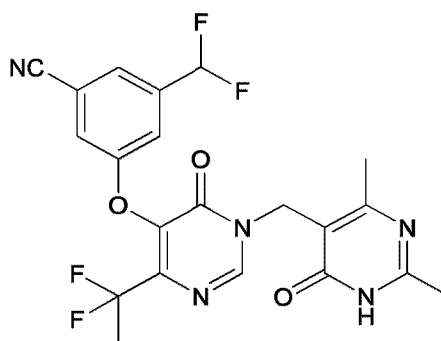
6. The compound of claim 5 that is



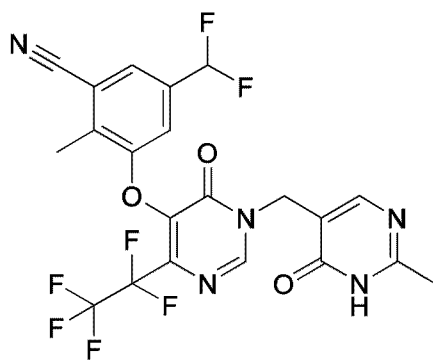
7. The compound of claim 1 that is



8. The compound of claim 7 that is

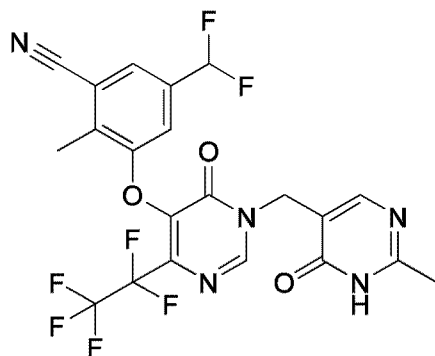


9. The compound of claim 1 that is

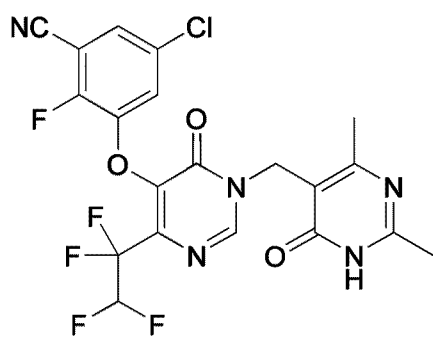


, or a pharmaceutically acceptable salt thereof.

10. The compound of claim 9 that is

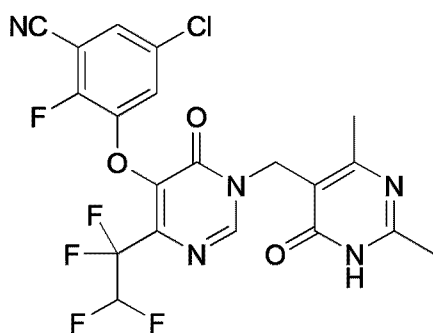


11. The compound of claim 1 that is



, or a pharmaceutically acceptable salt thereof.

12. The compound of claim 11 that is



13. A pharmaceutical composition comprising the compound according to any one of claims 1 to 3, 5, 7, 9 or 11 or a pharmaceutically acceptable salt thereof, or a compound according to any one of claims 4, 6, 8, 10 or 12, and a pharmaceutically acceptable carrier.

14. The pharmaceutical composition of claim 13 further comprising an effective amount of one or more additional nucleoside or nucleotide HIV reverse transcriptase inhibitors, nucleoside or nucleotide reverse transcriptase translocation inhibitors, non-nucleoside HIV reverse transcriptase inhibitors, HIV integrase inhibitors, HIV fusion inhibitors, HIV entry inhibitors, HIV maturation inhibitors and post-attachment inhibitors.

15. Use of an effective amount of the compound according to any one of claims 1 to 3, 5, 7, 9 or 11 or a pharmaceutically acceptable salt thereof, or a compound according to any one of claims 4, 6, 8, 10 or 12 for the treatment or prophylaxis of infection by

HIV, or for the treatment, prophylaxis or delay in the onset or progression of AIDS or ARC in a human subject in need thereof.

16. Use of an effective amount of the compound according to any one of claims 1 to 3, 5, 7, 9 or 11 or a pharmaceutically acceptable salt thereof, or a compound according to any one of claims 4, 6, 8, 10 or 12 for eliciting GAG-POL dimerization in HIV-infected cells in a human subject in need thereof.

17. Use of an effective amount of the compound according to any one of claims 1 to 3, 5, 7, 9 or 11 or a pharmaceutically acceptable salt thereof, or a compound according to any one of claims 4, 6, 8, 10 or 12 for selectively killing HIV infected GAG-POL expressing cells without concomitant cytotoxicity to HIV naïve cells in a human subject.

18. The use of any one of claims 15 to 17, wherein the compound or pharmaceutically acceptable salt thereof is formulated for an administration with an effective amount of one or more additional compatible HIV antiviral agent selected from nucleoside or nucleotide HIV reverse transcriptase inhibitors, nucleoside reverse transcriptase translocation inhibitors, non-nucleoside HIV reverse transcriptase inhibitors, HIV integrase inhibitors, HIV fusion inhibitors, HIV entry inhibitors, HIV maturation inhibitors and post-attachment inhibitors.

19. Use of an effective amount of the compound according to any one of claims 1 to 3, 5, 7, 9 or 11 or a pharmaceutically acceptable salt thereof, or a compound according to any one of claims 4, 6, 8, 10 or 12 for augmenting the suppression of HIV viremia in a human subject whose viremia is being suppressed by the administration of one or more compatible HIV antiviral agents.

20. Use of an effective amount of the compound according to any one of claims 1 to 3, 5, 7, 9 or 11 or a pharmaceutically acceptable salt thereof, or a compound according to any one of claims 4, 6, 8, 10 or 12 in the manufacture of a medicament for the

treatment or prophylaxis of infection by HIV, or for the treatment, prophylaxis or delay in the onset or progression of AIDS or ARC in a human subject in need thereof.

21. Use of an effective amount of the compound according to any one of claims 1 to 3, 5, 7, 9 or 11 or a pharmaceutically acceptable salt thereof, or a compound according to any one of claims 4, 6, 8, 10 or 12 in the manufacture of a medicament for eliciting GAG-POL dimerization in HIV-infected cells in a human subject in need thereof.

22. Use of an effective amount of the compound according to any one of claims 1 to 3, 5, 7, 9 or 11 or a pharmaceutically acceptable salt thereof, or a compound according to any one of claims 4, 6, 8, 10 or 12 in the manufacture of a medicament for selectively killing HIV infected GAG-POL expressing cells without concomitant cytotoxicity to HIV naïve cells in a human subject.

23. The use of any one of claims 20 to 22, wherein the compound or pharmaceutically acceptable salt thereof is formulated for an administration with an effective amount of one or more additional compatible HIV antiviral agent selected from nucleoside or nucleotide HIV reverse transcriptase inhibitors, nucleoside reverse transcriptase translocation inhibitors, non-nucleoside HIV reverse transcriptase inhibitors, HIV integrase inhibitors, HIV fusion inhibitors, HIV entry inhibitors, HIV maturation inhibitors and post-attachment inhibitors.

24. Use of an effective amount of the compound according to any one of claims 1 to 3, 5, 7, 9 or 11 or a pharmaceutically acceptable salt thereof, or a compound according to any one of claims 4, 6, 8, 10 or 12 in the manufacture of a medicament for augmenting the suppression of HIV viremia in a human subject whose viremia is being suppressed by the administration of one or more compatible HIV antiviral agents.

25. The use of any one of claims 15-24, wherein the HIV is HIV-1.

26. The compound according to any one of claims 1 to 3, 5, 7, 9 or 11 or a pharmaceutically acceptable salt thereof, or a compound according to any one of claims 4, 6, 8, 10 or 12, for the treatment or prophylaxis of infection by HIV, or for the treatment, prophylaxis or delay in the onset or progression of AIDS or ARC in a human subject.

27. The compound according to any one of claims 1 to 3, 5, 7, 9 or 11 or a pharmaceutically acceptable salt thereof, or a compound according to any one of claims 4, 6, 8, 10 or 12, for selectively killing HIV infected GAG-POL expressing cells without concomitant cytotoxicity to HIV naïve cells in a human subject.

28. The compound according to any one of claims 1 3, 5, 7, 9 or 11 or a pharmaceutically acceptable salt thereof, or a compound according to any one of claims 4, 6, 8, 10 or 12, for augmenting the suppression of HIV viremia in a human subject whose viremia is being suppressed by one or more compatible HIV antiviral agents.

29. The compound of any one of claims 26-28, wherein the HIV is HIV-1.

