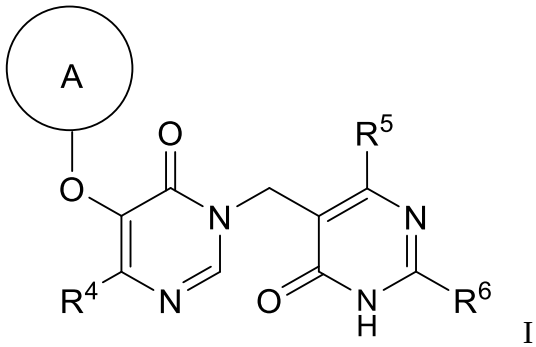
maturation so that virions produced from cells treated with protease inhibitors are immature and non-infectious. Once integration has occurred, a cell is infected until it dies through either normal cell death pathways, accelerated death due to viral factors, or is targeted by the immune system. While most infected cells are expected to die within ~2 days of being infected, the rapid 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 patients have the potential to decrease low-level viremia in suppressed patients and may also play a role in an HIV cure strategy.

SUMMARY

The present disclosure is directed to pyrimidone derivatives and their use as HIV-Targeted Activator of Cell Kill agents which accelerate the death of HIV GAG-POL expressing cells without concomitant cytotoxicity to HIV naïve cells.

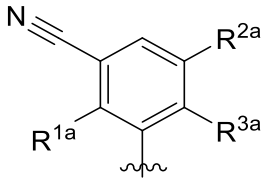
In one aspect, there is provided a compound of Formula I:



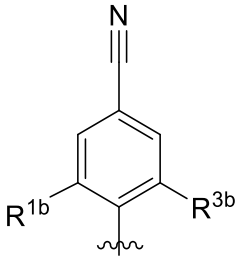
I

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is selected from:

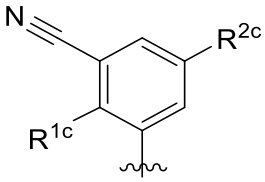


(Aa),



(Ab)

or



(Ac);

R^{1a} is halo, -C_{1-3}alkyl unsubstituted or substituted with 1 to 7 of F; -OC_{1-3}alkyl unsubstituted or substituted with 1 to 7 of F; or -NH_2, -NH-C_{1-3}alkyl, -N(C_{1-3}alkyl)$_2$, or -C_{3-6}cycloalkyl;

R^{2a} is -H, halo, -C_{1-3}alkyl, -CF_3, -CHF_2, -CH_2F, -OC_{1-3}alkyl, -NH_2, -NH-C_{1-3}alkyl, -N(C_{1-3}alkyl)$_2$, or -C_{3-6}cycloalkyl or -OC_{1-3}alkyl 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;

R^{1b} is halo, -C_{1-3}alkyl, -CF_3, -CHF_2, -CH_2F, -NH_2, -NH-C_{1-3}alkyl, -N(C_{1-3}alkyl)$_2$, -C_{3-6}cycloalkyl, or -OC_{1-3}alkyl unsubstituted or substituted with 1 to 3 of F;

R^{3b} is halo, -C_{1-3}alkyl, -CF_3, -CHF_2, -CH_2F, -NH_2, -NH-C_{1-3}alkyl, -N(C_{1-3}alkyl)$_2$, -C_{3-6}cycloalkyl, or -OC_{1-3} alkyl unsubstituted or substituted with 1 to 3 of F;

R^{1c} is -H, halo, -C_{1-3}alkyl, -CF_3, -CHF_2, -CH_2F, -NH_2, -NH-C_{1-3}alkyl, -N(C_{1-3}alkyl)$_2$, -C_{3-6}cycloalkyl, or -OC_{1-3}alkyl unsubstituted or substituted with 1 to 3 of F;

R^{2c} is -H, bromo, -C_{1-3}alkyl, -CF_3, -CHF_2, -CH_2F, -NH_2, -NH-C_{1-3}alkyl, -N(C_{1-3}alkyl)$_2$, -C_{3-6}cycloalkyl, or -OC_{1-3}alkyl 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;

R^4 is halo or -C_{1-6}alkyl substituted with 1 to 8 of -F;

R^5 is -H, -NH_2, -NH-C_{1-3}alkyl, -N(C_{1-3}alkyl)$_2$, -C_{3-6}cycloalkyl, or -C_{1-3}alkyl unsubstituted or substituted with 1 to 7 of -F;

R^6 is –H, -C_{1-4}alkyl, -C_{2-4}alkenyl, -NH_2, -NH-C_{1-3}alkyl, -N(C_{1-3}alkyl)$_2$, C_{3-6}cycloalkyl, -pyrazolyl unsubstituted or substituted with C_{1-3}alkyl, or -C_{1-4}alkyl substituted with R^7; and

R^7 is –OH, -OC_{1-3}alkyl, -C(O)OC_{1-3}alkyl or -CH_2O-pyrimidinyl.

In another aspect, there is provided a pharmaceutical composition comprising an effective amount of the compound as defined herein or a pharmaceutically acceptable salt thereof, or a compound as defined herein, and a pharmaceutically acceptable carrier.

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 expressing cells in a subject infected with HIV. Compositions and methods of use comprising the compounds of this disclosure are also provided.

In another aspect, there is provided use of the compound as defined herein or a pharmaceutically acceptable salt thereof, or a compound as defined herein 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.

In another aspect, there is provided use of the compound as defined herein or a pharmaceutically acceptable salt thereof, or a compound as defined herein in the manufacture of a medicament for for eliciting GAG-POL dimerization in HIV-infected cells in a human subject in need thereof.

In another aspect, there is provided use of the compound as defined herein or a pharmaceutically acceptable salt thereof, or a compound as defined herein 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.

In another aspect, there is provided use of the compound as defined herein or a pharmaceutically acceptable salt thereof, or a compound as defined herein in the manufacture of a medicament 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 agents.

In another aspect, there is provided a compound as defined herein or a pharmaceutically acceptable salt thereof, or a compound as defined herein, for use in the

treatment or prophylaxis of infection by HIV, or for use in the treatment, prophylaxis or delay in the onset or progression of AIDS or ARC in a human subject.

In another aspect, there is provided a compound as defined herein or a pharmaceutically acceptable salt thereof, or a compound as defined herein, for use in selectively killing HIV infected GAG-POL expressing cells without concomitant cytotoxicity to HIV naïve cells in a human subject.

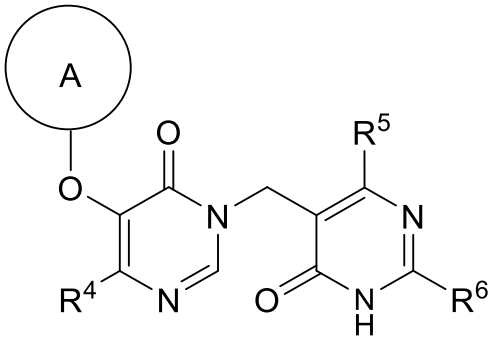
In another aspect, there is provided a compound as defined herein or a pharmaceutically acceptable salt thereof, or a compound as defined herein, for use in augmenting the suppression of HIV viremia in a human subject whose viremia is being suppressed by one or more compatible HIV antiviral agents.

DETAILED DESCRIPTION OF THE INVENTION

The present disclosure is directed to pyrimidone derivative compounds and their 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 immature RT binding site and triggering premature activation of the HIV PR enzyme inside the

WHAT IS CLAIMED IS:

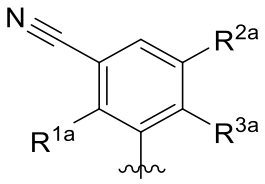
1. A compound of Formula I:



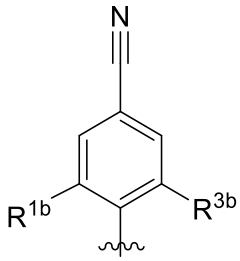
I

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is selected from:

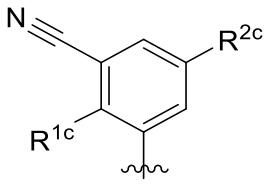


(Aa),



(Ab)

or



(Ac);

R^{1a} is halo, -C_{1-3}alkyl unsubstituted or substituted with 1 to 7 of F; -OC_{1-3}alkyl unsubstituted or substituted with 1 to 7 of F; or -NH_2, -NH-C_{1-3}alkyl, -N(C_{1-3}alkyl)$_2$, or -C_{3-6}cycloalkyl;

R^{2a} is -H, halo, -C_{1-3}alkyl, -CF_3, -CHF_2, -CH_2F, -OC_{1-3}alkyl, -NH_2, -NH-C_{1-3}alkyl, -N(C_{1-3}alkyl)$_2$, or -C_{3-6}cycloalkyl or -OC_{1-3}alkyl 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;

R^{1b} is halo, -C_{1-3}alkyl, -CF_3, -CHF_2, -CH_2F, -NH_2, -NH-C_{1-3}alkyl, -N(C_{1-3}alkyl)$_2$, -C_{3-6}cycloalkyl, or -OC_{1-3}alkyl unsubstituted or substituted with 1 to 3 of F;

R^{3b} is halo, -C_{1-3}alkyl, -CF_3, -CHF_2, -CH_2F, -NH_2, -NH-C_{1-3}alkyl, -N(C_{1-3}alkyl)$_2$, -C_{3-6}cycloalkyl, or -OC_{1-3} alkyl unsubstituted or substituted with 1 to 3 of F;

R^{1c} is -H, halo, -C_{1-3}alkyl, -CF_3, -CHF_2, -CH_2F, -NH_2, -NH-C_{1-3}alkyl, -N(C_{1-3}alkyl)$_2$, -C_{3-6}cycloalkyl, or -OC_{1-3}alkyl unsubstituted or substituted with 1 to 3 of F;

R^{2c} is -H, bromo, -C_{1-3}alkyl, -CF_3, -CHF_2, -CH_2F, -NH_2, -NH-C_{1-3}alkyl, -N(C_{1-3}alkyl)$_2$, -C_{3-6}cycloalkyl, or -OC_{1-3}alkyl 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;

R^4 is halo or -C_{1-6}alkyl substituted with 1 to 8 of -F;

R^5 is -H, -NH_2, -NH-C_{1-3}alkyl, -N(C_{1-3}alkyl)$_2$, -C_{3-6}cycloalkyl, or -C_{1-3}alkyl unsubstituted or substituted with 1 to 7 of -F;

R^6 is –H, -C_{1-4}alkyl, -C_{2-4}alkenyl, -NH_2, -NH-C_{1-3}alkyl, -N(C_{1-3}alkyl)$_2$, C_{3-6}cycloalkyl, -pyrazolyl unsubstituted or substituted with C_{1-3}alkyl, or -C_{1-4}alkyl substituted with R^7; and

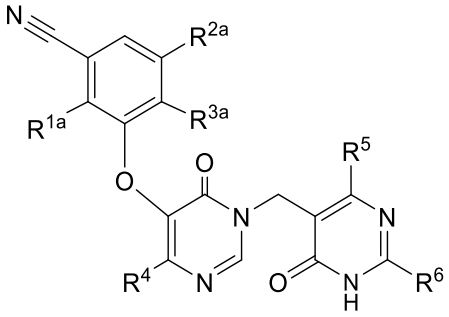
R^7 is –OH, -OC_{1-3}alkyl, -C(O)OC_{1-3}alkyl or -CH_2O-pyrimidinyl.

2. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein R^4 is -C_{1-6}alkyl substituted with 1 to 8 of –F.

3. The compound of claim 2 or a pharmaceutically acceptable salt thereof, wherein R^5 is -H, -NH_2, -C_{3-4}cycloalkyl, or -C_{1-3}alkyl unsubstituted or substituted with 1 to 7 of –F.

4. The compound of claim 3 or a pharmaceutically acceptable salt thereof, wherein R^6 is –H, -C_{1-4}alkyl, -CH=C(C_{1-3}alkyl)$_2$, -NH_2, -NH-C_{1-3}alkyl, -N(C_{1-3}alkyl)$_2$, or -C_{1-4}alkyl substituted with R^7; and R^7 is –OH, -OC_{1-3}alkyl or -C(O)OC_{1-3}alkyl.

5. The compound of any one of claims 1 to 4 having Formula Ia



Ia

or a pharmaceutically acceptable salt thereof.

6. The compound of claim 5 or a pharmaceutically acceptable salt thereof, wherein:

R^{1a} is -F, -Cl, Br, -C_{1-3}alkyl, -CF_3, -CHF_2, -CH_2F, -NH_2, -C_{3-4}cycloalkyl or -OC_{1-3}alkyl unsubstituted or substituted with 1 to 3 of F; and

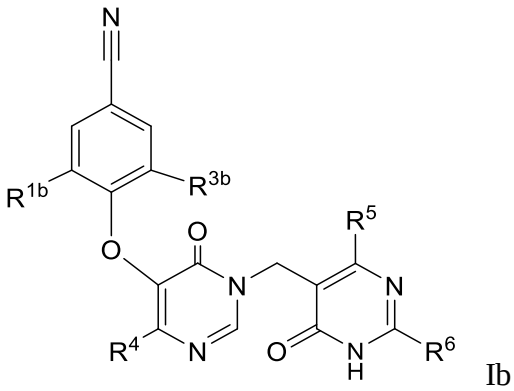
R^{2a} is -H, -F, -Cl, Br, -C_{1-3}alkyl, -CF_3, -CHF_2, -CH_2F, -NH_2, -C_{3-4}cycloalkyl or -OC_{1-3} alkyl unsubstituted or substituted with 1 to 3 of F; provided that R^{2a} and R^{3a} are not both –H.

7. The compound of claim 6 or a pharmaceutically acceptable salt thereof, wherein R^{3a} is –H, -F, -Cl or Br, provided that R^{2a} and R^{3a} are not both –H.

8. The compound of claim 6 or a pharmaceutically acceptable salt thereof, wherein R^4 is -CH(F)-R^8 or -$C(F_2)$-R^8, and

R^8 is (a) –CH_3 unsubstituted or substituted with 1 to 3 of –F, or (b) -CH_2CH_3 unsubstituted or substituted with 1 to 5 of –F.

9. The compound of any one of claims 1 to 4 having Formula Ib



Ib

or a pharmaceutically acceptable salt thereof.

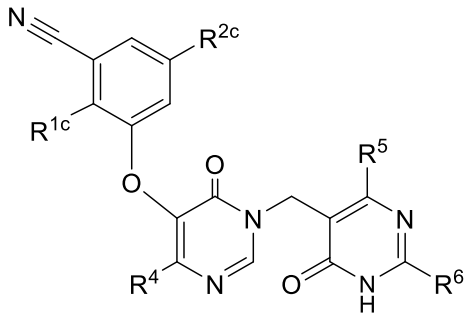
10. The compound of claim 9 or a pharmaceutically acceptable salt thereof, wherein R^{1b} and R^{3b} are each independently halo, -C_{1-3}alkyl, -CF_3, -CHF_2, -CH_2F, -OC_{1-3}alkyl, or -C_{3-4}cycloalkyl.

11. The compound of claim 9 or a pharmaceutically acceptable salt thereof, wherein R^{1b} and R^{3b} are each independently halo, -C_{1-3}alkyl, -CF_3, -CHF_2, -CH_2F, -C_{3-4}cycloalkyl, or -OC_{1-3}alkyl unsubstituted or substituted with 1 to 3 of F.

12. The compound of claim 9 or a pharmaceutically acceptable salt thereof, wherein R^{1b} and R^{3b} are each independently -F, -Cl, -CH_3, -CF_3, -CHF_2, -CH_2F, -OCH_3 or cyclopropyl.

13. The compound of claim 10 or a pharmaceutically acceptable salt thereof, wherein R^4 is -CF_3, -CH(F)-R^8 or -$C(F_2)$-R^8, and
R^8 is (a) –CH_3 unsubstituted or substituted with 1 to 3 of –F, or (b) -CH_2CH_3 unsubstituted or substituted with 1 to 5 of –F.

14. The compound of any one of claims 1 to 4 having Formula Ic



Ic

or a pharmaceutically acceptable salt thereof.

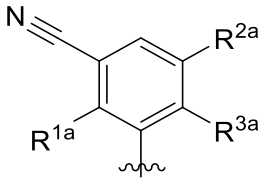
15. The compound of claim 14 or a pharmaceutically acceptable salt thereof, wherein R^{1c} is -H, halo, $-CH_3$, $-CF_3$, $-CHF_2$, or $-CH_2F$, provided that one of R^{1c} or R^{2c} is -H and the other is not –H.

16. The compound of claim 14 or a pharmaceutically acceptable salt thereof, wherein R^{2c} is -H, bromo, $-CH_3$, $-CF_3$, $-CHF_2$, or $-CH_2F$, provided that one of R^{1c} or R^{2c} is -H and the other is not –H.

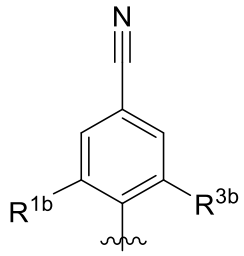
17. The compound of claim 15 or a pharmaceutically acceptable salt thereof, wherein R^{1c} is -H, halo , $-CH_3$, $-CF_3$, $-CHF_2$ or $-CH_2F$, and
R^{2c} is -H, bromo , $-CH_3$, $-CF_3$, $-CHF_2$ or $-CH_2F$, provided that one of R^{1c} or R^{2c} is -H and the other is not –H.

18. The compound of claim 15 or a pharmaceutically acceptable salt thereof, wherein R^4 is $-CH(F)-R^8$ or $-C(F_2)-R^8$, and
R^8 is (a) $–CH_3$ unsubstituted or substituted with 1 to 3 of –F, or (b) $-CH_2CH_3$ unsubstituted or substituted with 1 to 5 of –F.

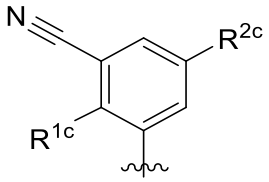
19. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein
Ring A is selected from:



(Aa),



(Ab)



(Ac);

or

R^{1a} is halo, -C_{1-3}alkyl, -OC_{1-3}alkyl unsubstituted or substituted with 1-3 of F, or -NH_2;

R^{2a} is -H, halo, -C_{1-3}alkyl unsubstituted or substituted with 1-6 of F;

R^{3a} is –H or halo;

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

R^{1b} is halo, -C_{1-3}alkyl, -OC_{1-3}alkyl, -CF_3, or -C_{3-6}cycloalkyl;

R^{3b} is halo or -C_{1-3}alkyl unsubstituted or substituted with 1-6 of F;

R^{1c} is -H, halo or -C_{1-3}alkyl;

R^{2c} is -H, bromo, -C_{1-3}alkyl unsubstituted or substituted with 1 to 6 of –F;

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

R^4 is halo, or -C_{1-3}alkyl substituted with 1 to 6 of –F;

R^5 is -H, -NH_2, -C_{3-6}cycloalkyl, or -C_{1-3}alkyl unsubstituted or substituted with 1 to 6 of –F;

R^6 is –H, -C_{1-3}alkyl, -C_{1-4}alkyl-OR^7, -C_{1-3}alkyl-COOH, -C_{2-4}alkenyl, -NH_2 and pyrazolyl unsubstituted or substituted with C_{1-3}alkyl,

wherein R^7 is -H, -C_{1-3}alkyl-OCH_3 or -CH_2O-pyrimidinyl.

20. The compound of claim 1 that is:

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;
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;
(*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;
(*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;
(*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;
(*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-fluorobenzonitrile,

(*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 ;
(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-methoxybenzonitrile;
(*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-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*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;
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;
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.

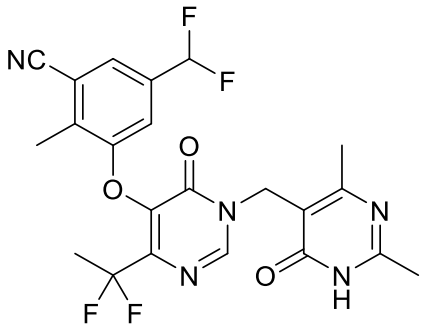
21. The compound of claim 1 that is:

(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 (*S*) and (*R*) 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 (*S*) and (*R*) 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 (*S*) and (*R*) 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; 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, and the (*S*) and (*R*) stereoisomers thereof;

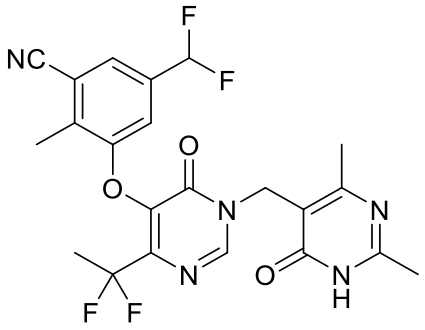
or a pharmaceutically acceptable salt thereof.

22. The compound of claim 1 that is



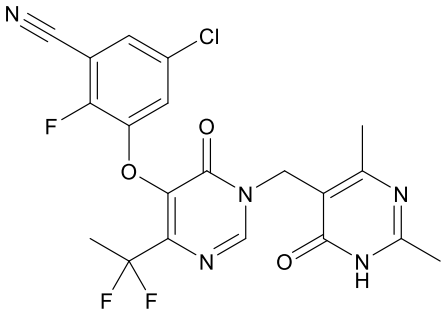
, or a pharmaceutically acceptable salt thereof.

23. The compound of claim 22 that is



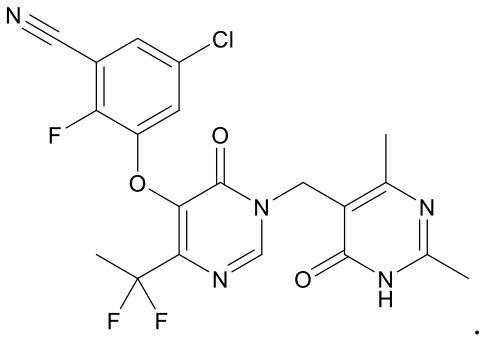
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24. The compound of claim 1 that is



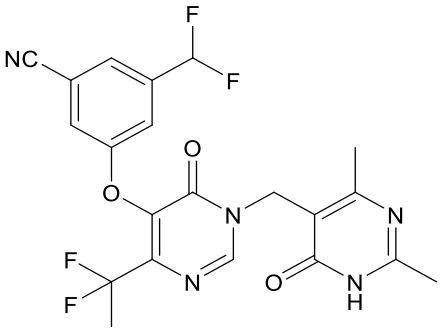
, or a pharmaceutically acceptable salt thereof.

25. The compound of claim 24 that is



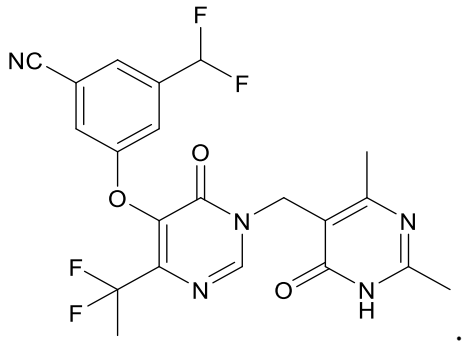
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26. The compound of claim 1 that is



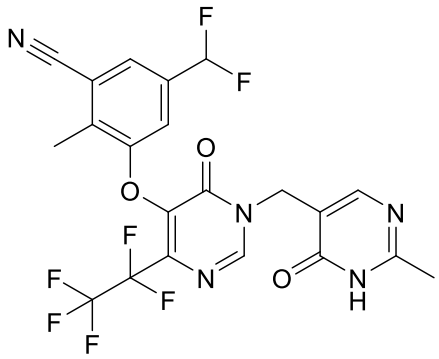
, or a pharmaceutically acceptable salt thereof.

27. The compound of claim 26 that is



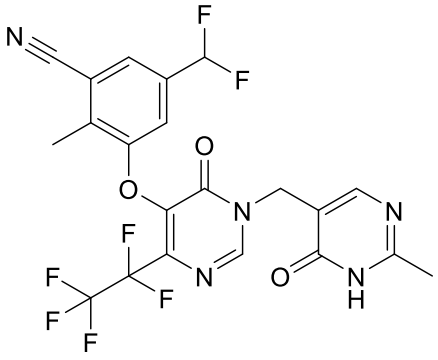
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28. The compound of claim 1 that is



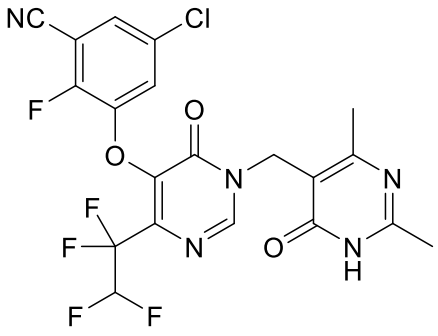
, or a pharmaceutically acceptable salt thereof.

29. The compound of claim 28 that is



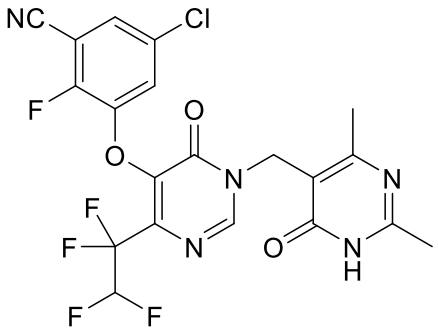
.

30. The compound of claim 1 that is



, or a pharmaceutically acceptable salt thereof.

31. The compound of claim 30 that is



.

32. A pharmaceutical composition comprising an effective amount of the compound according to any one of claims 1 to 22, 24, 26, 28 or 30 or a pharmaceutically acceptable salt thereof, or a compound according to any one of claims 23, 25, 27, 29 or 31, and a pharmaceutically acceptable carrier.

33. The pharmaceutical composition of claim 32 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.

34. Use of the compound according to any one of claims 1 to 22, 24, 26, 28 or 30 or a pharmaceutically acceptable salt thereof, or a compound according to any one of claims 23, 25, 27, 29 or 31 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.

35. Use of the compound according to any one of claims 1 to 22, 24, 26, 28 or 30 or a pharmaceutically acceptable salt thereof, or a compound according to any one of claims 23, 25, 27, 29 or 31 in the manufacture of a medicament for eliciting GAG-POL dimerization in HIV-infected cells in a human subject in need thereof.

36. Use of the compound according to any one of claims 1 to 22, 24, 26, 28 or 30 or a pharmaceutically acceptable salt thereof, or a compound according to any one of claims 23, 25, 27, 29 or 31 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.

37. The use of claim 34 to 36, wherein the medicament is to be administered to the human subject 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.

38. Use of the compound according to any one of claims 1 to 22, 24, 26, 28 or 30 or a pharmaceutically acceptable salt thereof, or a compound according to any one of claims 23, 25, 27, 29 or 31 in the manufacture of a medicament 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 agents.

39. A compound according to any one of claims 1 to 22, 24, 26, 28 or 30 or a pharmaceutically acceptable salt thereof, or a compound according to any one of claims 23, 25, 27, 29 or 31, for use in the treatment or prophylaxis of infection by HIV, or for use in the treatment, prophylaxis or delay in the onset or progression of AIDS or ARC in a human subject.

40. A compound according to any one of claims 1 to 22, 24, 26, 28 or 30 or a pharmaceutically acceptable salt thereof, or a compound according to any one of claims 23, 25, 27, 29 or 31, for use in selectively killing HIV infected GAG-POL expressing cells without concomitant cytotoxicity to HIV naïve cells in a human subject.

41. A compound according to any one of claims 1 to 22, 24, 26, 28 or 30 or a pharmaceutically acceptable salt thereof, or a compound according to any one of claims 23, 25, 27, 29 or 31, for use in augmenting the suppression of HIV viremia in a human subject whose viremia is being suppressed by one or more compatible HIV antiviral agents.

42. The use according to any one of claims 34 to 38 or the compound or a pharmaceutically acceptable salt thereof for use according to any one of claims 39 to 41 wherein the HIV is HIV-1.