

HIV INTEGRASE INHIBITORS: CYCLIC PYRIMIDINONE COMPOUNDS

CROSS REFERENCE TO RELATED APPLICATIONS

- 5 This application claims the benefit of U.S. provisional application number 60/570,348 filed May 12, 2004.

BACKGROUND OF THE INVENTION

- 10 Human immunodeficiency virus (HIV) has been identified as the etiological agent responsible for acquired immune deficiency syndrome (AIDS), a fatal disease characterized by destruction of the immune system and the inability to fight off life threatening opportunistic infections. Recent statistics (UNAIDS: Report on the Global HIV/AIDS Epidemic, December 1998), indicate that as many as 33 million
15 people worldwide are infected with the virus. In addition to the large number of individuals already infected, the virus continues to spread. Estimates from 1998 point to close to 6 million new infections in that year alone. In the same year there were approximately 2.5 million deaths associated with HIV and AIDS.
- 20 There are currently a number of antiviral drugs available to combat the infection. These drugs can be divided into three classes based on the viral protein they target and their mode of action. In particular, saquinavir, indinavir, ritonavir, nelfinavir and amprenavir are competitive inhibitors of the aspartyl protease expressed by HIV. Zidovudine, didanosine, stavudine, lamivudine, zalcitabine and
25 abacavir are nucleoside reverse transcriptase inhibitors that behave as substrate mimics to halt viral cDNA synthesis. And nevirapine, delavirdine and efavirenz are non-nucleoside reverse transcriptase inhibitors, which inhibit the synthesis of viral cDNA via a non-competitive (or uncompetitive) mechanism. When used alone these drugs are effective in reducing viral replication. The effect, however, is only
30 temporary as the virus readily develops resistance to all known agents. Currently, combination therapy has proven very effective at both reducing virus and suppressing the emergence of resistance in a number of patients. In the US, where combination therapy is widely available, the number of HIV-related deaths has declined (Palella,

F. J.; Delany, K. M.; Moorman, A. C.; Loveless, M. O.; Furher, J.; Satten, G. A.; Aschman, D. J.; Holmberg, S. D. *N. Engl. J. Med.* 1998, 338, 853-860).

Unfortunately, not all patients are responsive and a large number fail this
5 therapy. In fact, approximately 30-50% of patients ultimately fail combination
therapy. Treatment failure in most cases is caused by the emergence of viral
resistance. Viral resistance in turn is caused by the rapid turnover of HIV-1 during
the course of infection combined with a high viral mutation rate. Under these
circumstances incomplete viral suppression caused by insufficient drug potency, poor
10 compliance due to the complicated drug regiment as well as intrinsic
pharmacological barriers to exposure provides fertile ground for resistance to emerge.
More disturbing are recent findings which suggest that low-level replication
continues even when viral plasma levels have dropped below detectable levels (< 50
copies/ml) (Carpenter, C. C.; Cooper, D. A.; Fischl, M. A.; Gatell, J. M.; Gazzard, B.
15 G.; Hammer, S. M.; Hirsch, M. S.; Jacobsen, D. M.; Katzenstein, D. A.; Montaner, J.
S.; Richman, D. D.; Saag, M. S.; Schechter, M.; Schooley, R. T.; Thompson, M. A.;
Vella, S.; Yeni, P. G.; Volberding, P. A. *JAMA* 2000, 283, 381-390). Clearly there is
a need for new antiviral agents, preferably targeting other viral enzymes to reduce the
rate of resistance and suppress viral replication even further.

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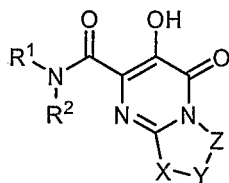
HIV expresses three enzymes: reverse transcriptase, an aspartyl protease, and
integrase. All three are targets for treating AIDS and HIV infection. HIV integrase
catalyzes insertion of the viral cDNA into the host cell genome, which is a critical
step in the viral life cycle. HIV integrase inhibitors belonging to a class of diketo
25 acid compounds prevented viral integration and inhibited HIV-1 replication in cells
(Hazuda et al. *Science* 2000, 287, 646). And recently, HIV integrase inhibitors have
been accepted into clinical trials for treating AIDS and HIV infection (Neamati
Expert. Opin. Ther. Patents 2002, 12, 709, Pais and Burke *Drugs Fut.* 2002, 27,
1101).

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DESCRIPTION OF THE INVENTION

The invention encompasses a series of pyrimidinone compounds which inhibit HIV integrase and thereby prevent viral integration into human DNA. This action makes the compounds useful for treating HIV infection and AIDS. The invention also encompasses intermediates useful for making the pyrimidone compounds. Additionally, pharmaceutical compositions and methods for treating those infected with HIV are encompassed.

One aspect of the invention is a compound of Formula I



I

where:

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R^1 is $C_{1-6}(Ar^1)alkyl$;

R^2 is hydrogen, $C_{1-6}alkyl$, or OR^6 ;

20 R^3 is hydrogen, halo, hydroxy, cyano, $C_{1-6}alkyl$, $C_{3-7}cycloalkyl$, $C_{1-6}haloalkyl$, $C_{1-6}alkoxy$, $C_{1-6}alkylthio$, $C_{1-6}haloalkoxy$, $CON(R^6)(R^6)$, SOR^7 , SO_2R^7 , $SO_2N(R^6)(R^6)$, or Ar^2 ;

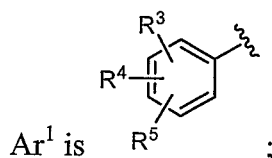
25 R^4 is hydrogen, halo, hydroxy, cyano, $C_{1-6}alkyl$, $C_{1-6}alkoxy$, $C_{1-6}haloalkyl$, or $C_{1-6}haloalkoxy$;

R^5 is hydrogen, halo, hydroxy, cyano, $C_{1-6}alkyl$, $C_{1-6}alkoxy$, $C_{1-6}haloalkyl$, or $C_{1-6}haloalkoxy$;

30 R^6 is hydrogen or $C_{1-6}alkyl$;

R^7 is C_{1-6} alkyl;

- R^8 and R^9 taken together are CH_2CH_2 , $CH_2CH_2CH_2$, $CH_2CH_2CH_2CH_2$,
 $CH_2CH_2CH_2CH_2CH_2$, $CH_2CH_2CH_2CH_2CH_2CH_2$, OCH_2CH_2 , CH_2OCH_2 ,
 5 $OCH_2CH_2CH_2$, $CH_2OCH_2CH_2$, $OCH_2CH_2CH_2CH_2$, $CH_2OCH_2CH_2CH_2$,
 $CH_2CH_2OCH_2CH_2$, $OCH_2CH_2CH_2CH_2CH_2$, $CH_2OCH_2CH_2CH_2CH_2$,
 $CH_2CH_2OCH_2CH_2CH_2$, $N(R^6)CH_2CH_2$, $CH_2N(R^6)CH_2$, $N(R^6)CH_2CH_2CH_2$,
 $CH_2N(R^6)CH_2CH_2$, $N(R^6)CH_2CH_2CH_2CH_2$, $CH_2N(R^6)CH_2CH_2CH_2$,
 $CH_2CH_2N(R^6)CH_2CH_2$, $N(R^6)CH_2CH_2CH_2CH_2CH_2$, $CH_2N(R^6)CH_2CH_2CH_2CH_2$, or
 10 $CH_2CH_2N(R^6)CH_2CH_2CH_2$;



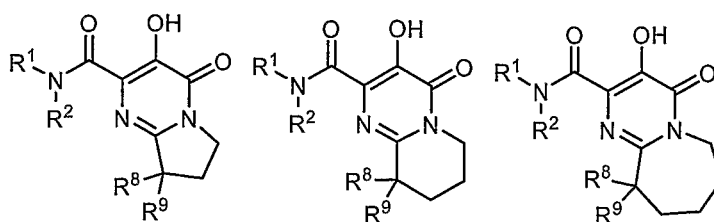
- Ar² is tetrazolyl, triazolyl, imidazolyl, pyrazolyl, pyrrolyl, or dioxothiazinyl, and is
 15 substituted with 0-2 substituents selected from the group consisting of amino, oxo,
 halo, cyano, and C_{1-6} alkyl; and

- X-Y-Z is $C(R^8)(R^9)CH_2CH_2$, $C(R^8)(R^9)CH_2CH_2CH_2$, $C(R^8)(R^9)CH_2CH_2CH_2CH_2$,
 $C(R^8)(R^9)OCH_2$, $C(R^8)(R^9)OCH_2CH_2$, or $C(R^8)(R^9)OCH_2CH_2CH_2$;
 20
 or a pharmaceutically acceptable salt or solvate thereof.

- Another aspect of the invention is a compound of Formula I where X-Y-Z is
 $C(R^8)(R^9)CH_2CH_2$, $C(R^8)(R^9)CH_2CH_2CH_2$, or $C(R^8)(R^9)CH_2CH_2CH_2CH_2$.
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Another aspect of the invention is a compound of Formula I according to the following structures.

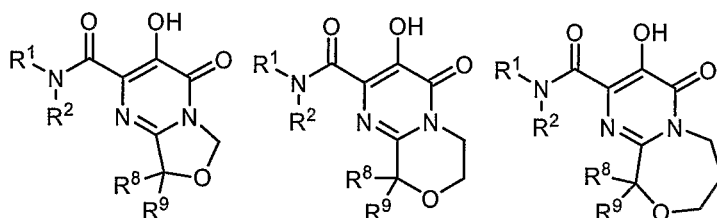
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Another aspect of the invention is a compound of Formula I where X-Y-Z is $C(R^8)(R^9)OCH_2$, $C(R^8)(R^9)OCH_2CH_2$, or $C(R^8)(R^9)OCH_2CH_2CH_2$.

5

Another aspect of the invention is a compound of Formula I according to the following structures.



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Another aspect of the invention is a compound of Formula I where R^8 and R^9 taken together are $CH_2CH_2CH_2$, $CH_2CH_2CH_2CH_2$, $CH_2CH_2CH_2CH_2CH_2$, $CH_2CH_2CH_2CH_2CH_2CH_2$, $CH_2OCH_2CH_2$, $CH_2CH_2OCH_2CH_2$, $CH_2N(R^6)CH_2CH_2$, or $CH_2CH_2N(R^6)CH_2CH_2$.

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Another aspect of the invention is a compound of Formula I where R^1 is $(Ar^1)methyl$.

Another aspect of the invention is a compound of Formula I where R^2 is hydrogen.

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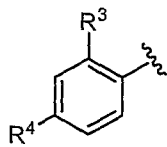
Another aspect of the invention is a compound of Formula I where R^3 is fluoro, chloro, methyl, $CON(R^6)(R^6)$, or Ar^2 .

Another aspect of the invention is a compound of Formula I where R^4 is hydrogen, fluoro, chloro, or methyl.

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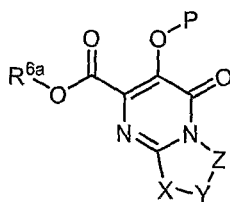
Another aspect of the invention is a compound of Formula I where R⁵ is hydrogen.

Another aspect of the invention is a compound of Formula I where Ar¹ is



For a compound of Formula I, any scope of R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸ and R⁹ taken together, and X-Y-Z can be used independently with any scope of any other substituent.

Another aspect of the invention is a compound of Formula II.



II

where

R^{6a} is hydrogen, C₁₋₆alkyl, C₁₋₆(Ar¹)alkyl, ArC₁₋₆, C-(C=C)_n-C, C₁₋₆-O-C₁₋₆-O-C₁₋₆, C₁₋₆-O-C₁₋₆-Ar, C(Ar)₂₋₃, CO(C₁₋₆)₁₋₃, or COAr; and

P is hydrogen, mesyl, tosyl, allyl, benzyl, fluorenylmethyl, allyloxycarbonyl, benzyloxycarbonyl, fluorenylmethoxycarbonyl, tri(C₁₋₆alkyl)silyl, C₁₋₆alkyl, C₁₋₆alkylcarbonyl, or C₁₋₆alkoxycarbonyl, ArC₁₋₆, C-(C=C)_n-C, C₁₋₆-O-C₁₋₆-O-C₁₋₆, C₁₋₆-O-C₁₋₆-Ar, CO(C₁₋₆)₁₋₃, COAr, or C(Ar)₂₋₃.

Another aspect of the invention is a compound of Formula II where R^{6a} is hydrogen, C₁₋₆alkyl, or C₁₋₆(Ar¹)alkyl; and P is hydrogen, mesyl, tosyl, allyl, benzyl,

fluorenylmethyl, allyloxycarbonyl, benzyloxycarbonyl, fluorenylmethoxycarbonyl, tri(C₁₋₆alkyl)silyl C₁₋₆alkyl, C₁₋₆alkylcarbonyl, or C₁₋₆alkoxycarbonyl.

Some compounds of the invention are

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N-[(4-fluorophenyl)methyl]-7',8'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclopentane-1,9'(6'H)-[4H]pyrido[1,2-*a*]pyrimidine]-2'-carboxamide;

10 *N*-[(4-fluoro-3-methylphenyl)methyl]-7',8'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclopentane-1,9'(6'H)-[4H]pyrido[1,2-*a*]pyrimidine]-2'-carboxamide;

N-[[2-(1*H*-1,2,4-triazol-1-yl)phenyl]methyl]-7',8'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclopentane-1,9'(6'*H*)-[4*H*]pyrido[1,2-*a*]pyrimidine]-2'-carboxamide;

15 *N*-[[4-fluoro-2-(1*H*-1,2,4-triazol-1-yl)phenyl]methyl]-7',8'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclopentane-1,9'(6'*H*)-[4*H*]pyrido[1,2-*a*]pyrimidine]-2'-carboxamide;

20 *N*-[[5-fluoro-2-(1*H*-1,2,4-triazol-1-yl)phenyl]methyl]-7',8'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclopentane-1,9'(6'*H*)-[4*H*]pyrido[1,2-*a*]pyrimidine]-2'-carboxamide;

25 *N*-[[4-fluoro-2-(2*H*-1,2,3-triazol-2-yl)phenyl]methyl]-7',8'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclopentane-1,9'(6'*H*)-[4*H*]pyrido[1,2-*a*]pyrimidine]-2'-carboxamide;

N-[[4-fluoro-2-(1*H*-imidazol-1-yl)phenyl]methyl]-7',8'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclopentane-1,9'(6'*H*)-[4*H*]pyrido[1,2-*a*]pyrimidine]-2'-carboxamide;

30 *N*-[[2-(tetrahydro-1,1-dioxido-2*H*-1,2-thiazin-2-yl)phenyl]methyl]-7',8'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclopentane-1,9'(6'*H*)-[4*H*]pyrido[1,2-*a*]pyrimidine]-2'-carboxamide;

N-[[4-fluoro-2-(tetrahydro-1,1-dioxido-2*H*-1,2-thiazin-2-yl)phenyl]methyl]-7',8'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclopentane-1,9'(6'*H*)-[4*H*]pyrido[1,2-*a*]pyrimidine]-2'-carboxamide;

5 *N*-[[2-[(dimethylamino)sulfonyl]-4-fluorophenyl]methyl]-7',8'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclopentane-1,9'(6'*H*)-[4*H*]pyrido[1,2-*a*]pyrimidine]-2'-carboxamide;

10 *N*-[[4-fluoro-2-(methylsulfonyl)phenyl]methyl]-7',8'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclopentane-1,9'(6'*H*)-[4*H*]pyrido[1,2-*a*]pyrimidine]-2'-carboxamide;

15 *N*-[[3-fluoro-2-(1*H*-1,2,4-triazol-1-yl)phenyl]methyl]-7',8'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclopentane-1,9'(6'*H*)-[4*H*]pyrido[1,2-*a*]pyrimidine]-2'-carboxamide;

N-(phenylmethyl)-7',8'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclobutane-1,9'(6'*H*)-[4*H*]pyrido[1,2-*a*]pyrimidine]-2'-carboxamide;

20 *N*-[(4-methylphenyl)methyl]-7',8'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclobutane-1,9'(6'*H*)-[4*H*]pyrido[1,2-*a*]pyrimidine]-2'-carboxamide;

N-[(4-methoxyphenyl)methyl]-7',8'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclobutane-1,9'(6'*H*)-[4*H*]pyrido[1,2-*a*]pyrimidine]-2'-carboxamide;

25 *N*-[(4-chlorophenyl)methyl]-7',8'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclobutane-1,9'(6'*H*)-[4*H*]pyrido[1,2-*a*]pyrimidine]-2'-carboxamide;

N-[(4-fluorophenyl)methyl]-7',8'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclobutane-1,9'(6'*H*)-[4*H*]pyrido[1,2-*a*]pyrimidine]-2'-carboxamide;

30 *N*-[(3-fluorophenyl)methyl]-7',8'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclobutane-1,9'(6'*H*)-[4*H*]pyrido[1,2-*a*]pyrimidine]-2'-carboxamide;

N-[(2-fluorophenyl)methyl]-7',8'-dihydro-3'-hydroxy-4'-oxo-
spiro[cyclobutane-1,9'(6'*H*)-[4*H*]pyrido[1,2-*a*]pyrimidine]-2'-carboxamide;

5 *N*-[(3,4-dimethylphenyl)methyl]-7',8'-dihydro-3'-hydroxy-4'-oxo-
spiro[cyclobutane-1,9'(6'*H*)-[4*H*]pyrido[1,2-*a*]pyrimidine]-2'-carboxamide;

N-[(3,4-dichlorophenyl)methyl]-7',8'-dihydro-3'-hydroxy-4'-oxo-
spiro[cyclobutane-1,9'(6'*H*)-[4*H*]pyrido[1,2-*a*]pyrimidine]-2'-carboxamide;

10 *N*-[(2,4-dimethoxyphenyl)methyl]-7',8'-dihydro-3'-hydroxy-4'-oxo-
spiro[cyclobutane-1,9'(6'*H*)-[4*H*]pyrido[1,2-*a*]pyrimidine]-2'-carboxamide;

N-[(4-fluoro-3-methylphenyl)methyl]-7',8'-dihydro-3'-hydroxy-4'-oxo-
spiro[cyclobutane-1,9'(6'*H*)-[4*H*]pyrido[1,2-*a*]pyrimidine]-2'-carboxamide;

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N-[(3-fluoro-4-methylphenyl)methyl]-7',8'-dihydro-3'-hydroxy-4'-oxo-
spiro[cyclobutane-1,9'(6'*H*)-[4*H*]pyrido[1,2-*a*]pyrimidine]-2'-carboxamide;

20 *N*-[1-(4-fluorophenyl)ethyl]-7',8'-dihydro-3'-hydroxy-4'-oxo-
spiro[cyclobutane-1,9'(6'*H*)-[4*H*]pyrido[1,2-*a*]pyrimidine]-2'-carboxamide;

N-[(2,5-difluorophenyl)methyl]-7',8'-dihydro-3'-hydroxy-4'-oxo-
spiro[cyclobutane-1,9'(6'*H*)-[4*H*]pyrido[1,2-*a*]pyrimidine]-2'-carboxamide;

25 *N*-[(2,5-dichlorophenyl)methyl]-7',8'-dihydro-3'-hydroxy-4'-oxo-
spiro[cyclobutane-1,9'(6'*H*)-[4*H*]pyrido[1,2-*a*]pyrimidine]-2'-carboxamide;

N-[[5-fluoro-2-(1*H*-1,2,4-triazol-1-yl)phenyl]methyl]-7',8'-dihydro-3'-
hydroxy-4'-oxo-spiro[cyclobutane-1,9'(6'*H*)-[4*H*]pyrido[1,2-*a*]pyrimidine]-2'-
30 carboxamide;

N-[[4-fluoro-2-(1*H*-1,2,4-triazol-1-yl)phenyl]methyl]-7',8'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclobutane-1,9'(6'*H*)-[4*H*]pyrido[1,2-*a*]pyrimidine]-2'-carboxamide;

- 5 *N*-[[4-fluoro-2-(tetrahydro-1,1-dioxido-2*H*-1,2-thiazin-2-yl)phenyl]methyl]-7',8'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclobutane-1,9'(6'*H*)-[4*H*]pyrido[1,2-*a*]pyrimidine]-2'-carboxamide;

- 10 *N*-[[2-(1*H*-1,2,4-triazol-1-yl)phenyl]methyl]-7',8'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclobutane-1,9'(6'*H*)-[4*H*]pyrido[1,2-*a*]pyrimidine]-2'-carboxamide;

N-[[4-fluoro-2-(methylsulfonyl)phenyl]methyl]-7',8'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclobutane-1,9'(6'*H*)-[4*H*]pyrido[1,2-*a*]pyrimidine]-2'-carboxamide;

- 15 *N*-[[2-[(dimethylamino)sulfonyl]-4-fluorophenyl]methyl]-7',8'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclobutane-1,9'(6'*H*)-[4*H*]pyrido[1,2-*a*]pyrimidine]-2'-carboxamide;

- 20 7',8'-dihydro-3'-hydroxy-4'-oxo-*N*-[[2-(tetrahydro-1,1-dioxido-2*H*-1,2-thiazin-2-yl)phenyl]methyl]-spiro[cyclobutane-1,9'(6'*H*)-[4*H*]pyrido[1,2-*a*]pyrimidine]-2'-carboxamide;

- 25 *N*-[(4-fluorophenyl)methyl]-6',7'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclopentane-1,8'(4'*H*)-pyrrolo[1,2-*a*]pyrimidine]-2'-carboxamide;

N-[[4-fluoro-2-(methylsulfonyl)phenyl]methyl]-6',7'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclopentane-1,8'(4'*H*)-pyrrolo[1,2-*a*]pyrimidine]-2'-carboxamide;

- 30 *N*-[[2-[(dimethylamino)sulfonyl]-4-fluorophenyl]methyl]-6',7'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclopentane-1,8'(4'*H*)-pyrrolo[1,2-*a*]pyrimidine]-2'-carboxamide;

N-[[4-fluoro-2-(1*H*-1,2,4-triazol-1-yl)phenyl]methyl]-6',7'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclopentane-1,8'(4'*H*)-pyrrolo[1,2-*a*]pyrimidine]-2'-carboxamide;

5 *N*-[(4-fluorophenyl)methyl]-2,3,5,6,7',8'-hexahydro-3'-hydroxy-4'-oxo-spiro[4*H*-pyran-4,9'(6'*H*)-[4*H*]pyrido[1,2-*a*]pyrimidine]-2'-carboxamide;

N-(phenylmethyl)-6',7'-dihydro-3'-hydroxy-4'-oxo- spiro[cyclopentane-1,9'(4'*H*)-pyrimido[2,1-*c*][1,4]oxazine]-2'-carboxamide;

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N-[(4-fluorophenyl)methyl]-6',7'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclopentane-1,9'(4'*H*)-pyrimido[2,1-*c*][1,4]oxazine]-2'-carboxamide;

15 *N*-[(4-fluoro-3-methylphenyl)methyl]-6',7'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclopentane-1,9'(4'*H*)-pyrimido[2,1-*c*][1,4]oxazine]-2'-carboxamide;

N-[[4-fluoro-2-(1*H*-1,2,4-triazol-1-yl)phenyl]methyl]-6',7'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclopentane-1,9'(4'*H*)-pyrimido[2,1-*c*][1,4]oxazine]-2'-carboxamide;

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N-[[4-fluoro-2-(methylthio)phenyl]methyl]-6',7'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclopentane-1,9'(4'*H*)-pyrimido[2,1-*c*][1,4]oxazine]-2'-carboxamide;

25 6',7'-dihydro-3'-hydroxy-*N*-[(4-methylphenyl)methyl]-4'-oxo-spiro[cyclopentane-1,9'(4'*H*)-pyrimido[2,1-*c*][1,4]oxazine]-2'-carboxamide;

N-[(4-chlorophenyl)methyl]-6',7'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclopentane-1,9'(4'*H*)-pyrimido[2,1-*c*][1,4]oxazine]-2'-carboxamide;

30 *N*-[(3,4-dichlorophenyl)methyl]-6',7'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclopentane-1,9'(4'*H*)-pyrimido[2,1-*c*][1,4]oxazine]-2'-carboxamide;

N-[(3,4-dimethylphenyl)methyl]-6',7'-dihydro-3'-hydroxy-4'-oxo-
spiro[cyclopentane-1,9'(4'H)-pyrimido[2,1-c][1,4]oxazine]-2'-carboxamide;

5 6',7'-dihydro-3'-hydroxy-N-[(4-methoxyphenyl)methyl]-4'-oxo-
spiro[cyclopentane-1,9'(4'H)-pyrimido[2,1-c][1,4]oxazine]-2'-carboxamide;

N-[(2-fluorophenyl)methyl]-6',7'-dihydro-3'-hydroxy-4'-oxo-
spiro[cyclopentane-1,9'(4'H)-pyrimido[2,1-c][1,4]oxazine]-2'-carboxamide;

10 N-[(2,4-dimethoxyphenyl)methyl]-6',7'-dihydro-3'-hydroxy-4'-oxo-
spiro[cyclopentane-1,9'(4'H)-pyrimido[2,1-c][1,4]oxazine]-2'-carboxamide;

N-[(3-fluorophenyl)methyl]-6',7'-dihydro-3'-hydroxy-4'-oxo-
spiro[cyclopentane-1,9'(4'H)-pyrimido[2,1-c][1,4]oxazine]-2'-carboxamide;

15

N-[(3-fluoro-4-methylphenyl)methyl]-6',7'-dihydro-3'-hydroxy-4'-oxo-
spiro[cyclopentane-1,9'(4'H)-pyrimido[2,1-c][1,4]oxazine]-2'-carboxamide;

20 N-[(2-(dimethylamino)sulfonyl)-4-fluorophenyl)methyl]-6',7'-dihydro-3'-
hydroxy-4'-oxo-spiro[cyclopentane-1,9'(4'H)-pyrimido[2,1-c][1,4]oxazine]-2'-
carboxamide;

25 N-[[5-fluoro-2-(1*H*-1,2,4-triazol-1-yl)phenyl]methyl]-6',7'-dihydro-3'-
hydroxy-4'-oxo-spiro[cyclopentane-1,9'(4'H)-pyrimido[2,1-c][1,4]oxazine]-2'-
carboxamide;

N-[2-(4-fluorophenyl)ethyl]-6',7'-dihydro-3'-hydroxy-4'-oxo-
spiro[cyclopentane-1,9'(4'H)-pyrimido[2,1-c][1,4]oxazine]-2'-carboxamide;

30 N-[3-(4-fluorophenyl)propyl]-6',7'-dihydro-3'-hydroxy-4'-oxo-
spiro[cyclopentane-1,9'(4'H)-pyrimido[2,1-c][1,4]oxazine]-2'-carboxamide;

N-[[4-fluoro-2-(5-methyl-1*H*-1,2,4-triazol-1-yl)phenyl]methyl]-6',7'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclopentane-1,9'(4'*H*)-pyrimido[2,1-*c*][1,4]oxazine]-2'-carboxamide;

5 6',7'-dihydro-3'-hydroxy-4'-oxo-*N*-[[2-(1*H*-1,2,4-triazol-1-yl)phenyl]methyl]-spiro[cyclopentane-1,9'(4'*H*)-pyrimido[2,1-*c*][1,4]oxazine]-2'-carboxamide;

N-[[4-fluoro-2-(tetrahydro-1,1-dioxido-2*H*-1,2-thiazin-2-yl)phenyl]methyl]-6',7'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclopentane-1,9'(4'*H*)-pyrimido[2,1-
10 *c*][1,4]oxazine]-2'-carboxamide;

6',7'-dihydro-3'-hydroxy-4'-oxo-*N*-[[2-(tetrahydro-1,1-dioxido-2*H*-1,2-thiazin-2-yl)phenyl]methyl]-spiro[cyclopentane-1,9'(4'*H*)-pyrimido[2,1-*c*][1,4]oxazine]-2'-carboxamide;

15 *N*-[(4-fluorophenyl)methyl]-4,5,6',7'-tetrahydro-3'-hydroxy-4'-oxo-spiro[furan-3(2*H*),9'(4'*H*)-pyrimido[2,1-*c*][1,4]oxazine]-2'-carboxamide;

N-[(4-fluoro-3-methylphenyl)methyl]-4,5,6',7'-tetrahydro-3'-hydroxy-4'-oxo-spiro[furan-3(2*H*),9'(4'*H*)-pyrimido[2,1-*c*][1,4]oxazine]-2'-carboxamide;

20 *N*-[[4-fluoro-2-(1*H*-1,2,4-triazol-1-yl)phenyl]methyl]-4,5,6',7'-tetrahydro-3'-hydroxy-4'-oxo-spiro[furan-3(2*H*),9'(4'*H*)-pyrimido[2,1-*c*][1,4]oxazine]-2'-carboxamide;

25 *N*-[[4-fluoro-2-(methylthio)phenyl]methyl]-4,5,6',7'-tetrahydro-3'-hydroxy-4'-oxo-spiro[furan-3(2*H*),9'(4'*H*)-pyrimido[2,1-*c*][1,4]oxazine]-2'-carboxamide;

N-[(4-fluorophenyl)methyl]-2,3,5,6,6',7'-hexahydro-3'-hydroxy-4'-oxo-spiro[4*H*-pyran-4,9'(4'*H*)-pyrimido[2,1-*c*][1,4]oxazine]-2'-carboxamide;

30

N-[[4-fluoro-2-(1*H*-1,2,4-triazol-1-yl)phenyl]methyl]-2,3,5,6,6',7'-hexahydro-3'-hydroxy-4'-oxo-spiro[4*H*-pyran-4,9'(4'*H*)-pyrimido[2,1-*c*][1,4]oxazine]-2'-carboxamide;

5 *N*-[[4-fluoro-2-(tetrahydro-1,1-dioxido-2*H*-1,2-thiazin-2-yl)phenyl]methyl]-2,3,5,6,6',7'-hexahydro-3'-hydroxy-4'-oxo-spiro[4*H*-pyran-4,9'(4'*H*)-pyrimido[2,1-*c*][1,4]oxazine]-2'-carboxamide;

10 *N*-[[2-(tetrahydro-1,1-dioxido-2*H*-1,2-thiazin-2-yl)phenyl]methyl]-2,3,5,6,6',7'-hexahydro-3'-hydroxy-4'-oxo-spiro[4*H*-pyran-4,9'(4'*H*)-pyrimido[2,1-*c*][1,4]oxazine]-2'-carboxamide;

15 *N*-[[4-fluoro-2-(methylsulfonyl)phenyl]methyl]-2,3,5,6,6',7'-hexahydro-3'-hydroxy-4'-oxo-spiro[4*H*-pyran-4,9'(4'*H*)-pyrimido[2,1-*c*][1,4]oxazine]-2'-carboxamide;

N-[(4-fluoro-3-methylphenyl)methyl]-2,3,5,6,6',7'-hexahydro-3'-hydroxy-4'-oxo-spiro[4*H*-pyran-4,9'(4'*H*)-pyrimido[2,1-*c*][1,4]oxazine]-2'-carboxamide;

20 *N*-[(2,4-dimethoxyphenyl)methyl]-2,3,5,6,6',7'-hexahydro-3'-hydroxy-4'-oxo-spiro[4*H*-pyran-4,9'(4'*H*)-pyrimido[2,1-*c*][1,4]oxazine]-2'-carboxamide;

25 *N*-[[2-[(dimethylamino)sulfonyl]-4-fluorophenyl]methyl]-2,3,5,6,6',7'-hexahydro-3'-hydroxy-4'-oxo-spiro[4*H*-pyran-4,9'(4'*H*)-pyrimido[2,1-*c*][1,4]oxazine]-2'-carboxamide

N-[(3,4-dimethylphenyl)methyl]-2,3,5,6,6',7'-hexahydro-3'-hydroxy-4'-oxo-spiro[4*H*-pyran-4,9'(4'*H*)-pyrimido[2,1-*c*][1,4]oxazine]-2'-carboxamide;

30 *N*-[[4-fluoro-2-(5-methyl-1*H*-1,2,4-triazol-1-yl)phenyl]methyl]-2,3,5,6,6',7'-hexahydro-3'-hydroxy-4'-oxo-spiro[4*H*-pyran-4,9'(4'*H*)-pyrimido[2,1-*c*][1,4]oxazine]-2'-carboxamide;

N-[[4-fluoro-2-(3-methyl-1*H*-1,2,4-triazol-1-yl)phenyl]methyl]-2,3,5,6,6',7'-hexahydro-3'-hydroxy-4'-oxo-spiro[4*H*-pyran-4,9'(4'*H*)-pyrimido[2,1-*c*][1,4]oxazine]-2'-carboxamide;

5 *N*-[[4-fluoro-2-(1*H*-1,2,4-triazol-1-yl)phenyl]methyl]-6',7'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclobutane-1,9'(4'*H*)-pyrimido[2,1-*c*][1,4]oxazine]-2'-carboxamide;

10 *N*-[(4-fluorophenyl)methyl]-6',7'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclobutane-1,9'(4'*H*)-pyrimido[2,1-*c*][1,4]oxazine]-2'-carboxamide;

N-[[4-fluoro-2-(methylsulfonyl)phenyl]methyl]-6',7'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclobutane-1,9'(4'*H*)-pyrimido[2,1-*c*][1,4]oxazine]-2'-carboxamide;

15 *N*-[[2-[(dimethylamino)sulfonyl]-4-fluorophenyl]methyl]-6',7'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclobutane-1,9'(4'*H*)-pyrimido[2,1-*c*][1,4]oxazine]-2'-carboxamide;

20 *N*-[[4-fluoro-2-(tetrahydro-1,1-dioxido-2*H*-1,2-thiazin-2-yl)phenyl]methyl]-6',7'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclobutane-1,9'(4'*H*)-pyrimido[2,1-*c*][1,4]oxazine]-2'-carboxamide;

25 *N*-[[2-(tetrahydro-1,1-dioxido-2*H*-1,2-thiazin-2-yl)phenyl]methyl]-6',7'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclobutane-1,9'(4'*H*)-pyrimido[2,1-*c*][1,4]oxazine]-2'-carboxamide;

N-[[4-fluoro-2-(5-methyl-1*H*-1,2,4-triazol-1-yl)phenyl]methyl]-6',7'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclobutane-1,9'(4'*H*)-pyrimido[2,1-*c*][1,4]oxazine]-2'-carboxamide;

30

N-[[4-fluoro-2-(methylsulfonyl)phenyl]methyl]-7',8'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclobutane-1,10'(4'*H*)-[6*H*]pyrimido[2,1-*c*][1,4]oxazepine]-2'-carboxamide;

N-[(4-fluorophenyl)methyl]-7',8'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclobutane-1,10'(4'H)-[6H]pyrimido[2,1-c][1,4]oxazepine]-2'-carboxamide;

5 *N*-[[4-fluoro-2-(1H-1,2,4-triazol-1-yl)phenyl]methyl]-7',8'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclobutane-1,10'(4'H)-[6H]pyrimido[2,1-c][1,4]oxazepine]-2'-carboxamide;

10 *N*-[[2-[(dimethylamino)sulfonyl]-4-fluorophenyl]methyl]-7',8'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclobutane-1,10'(4'H)-[6H]pyrimido[2,1-c][1,4]oxazepine]-2'-carboxamide;

N-[(4-fluorophenyl)methyl]-6',7'-dihydro-3'-hydroxy-4'-oxo-spiro[piperidine-4,9'(4'H)-pyrimido[2,1-c][1,4]oxazine]-2'-carboxamide

15 *N*-[[4-fluoro-2-(methylsulfonyl)phenyl]methyl]-6',7'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclopentane-1,9'(4'H)-pyrimido[2,1-c][1,4]oxazine]-2'-carboxamide;

20 *N*-[[4-fluoro-2-(methylsulfonyl)phenyl]methyl]-4,5,6',7'-tetrahydro-3'-hydroxy-4'-oxo-spiro[furan-3(2H),9'(4'H)-pyrimido[2,1-c][1,4]oxazine]-2'-carboxamide; and

25 *N*-[[4-fluoro-2-[(methylamino)carbonyl]phenyl]methyl]-6',7'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclobutane-1,9'(4'H)-pyrimido[2,1-c][1,4]oxazine]-2'-carboxamide;

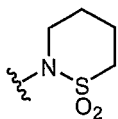
and salts and solvates of these compounds.

30 “Alkyl,” “alkoxy,” “haloalkyl,” and related terms for other hydrocarbon and substituted hydrocarbon substituents include straight and branched isomeric configurations. A term such as “C₁₋₆(R)alkyl” means a straight or branched alkyl group of 1 to 6 carbons substituted with the substituent R. “Haloalkyl” and related terms for halogenated substituents include all permutations of halogenation, from monohaloalkyl to perhaloalkyl. “Aryl” means an aromatic ring system and includes

carbocyclic and heterocyclic systems. Some substituents are divalent, for example, X-Y-Z. Divalent substituents which are asymmetric can be attached to the parent molecule in either of the configurations.

5

“Dioxothiazinyl” means



10

15

The invention includes all pharmaceutically acceptable salt forms of the compounds. Pharmaceutically acceptable salts are those in which the counter ions do not contribute significantly to the physiological activity or toxicity of the compounds and as such function as pharmacological equivalents. These salts can be made according to common organic techniques employing commercially available reagents. Some anionic salt forms include acetate, acistrate, besylate, bromide, chloride, citrate, fumarate, glucouronate, hydrobromide, hydrochloride, hydroiodide, iodide, lactate, maleate, mesylate, nitrate, pamoate, phosphate, succinate, sulfate, tartrate, tosylate, and xinofoate. Some cationic salt forms include ammonium, aluminum, benzathine, bismuth, calcium, choline, diethylamine, diethanolamine, lithium, magnesium, meglumine, 4-phenylcyclohexylamine, piperazine, potassium, sodium, tromethamine, and zinc.

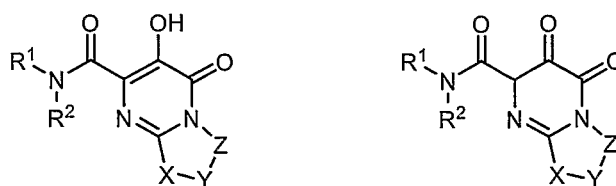
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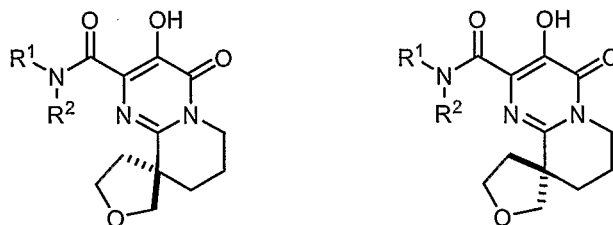
The invention also includes all solvated forms of the compounds, particularly hydrates. Solvates do not contribute significantly to the physiological activity or toxicity of the compounds and as such function as pharmacological equivalents. Solvates may form in stoichiometric amounts or may form from adventitious solvent or a combination of both. One type of solvate is hydrate, and some hydrated forms include monohydrate, hemihydrate, and dihydrate.

The invention includes all tautomeric forms of the compounds. An example of a tautomeric pair is shown below.

18



Some of the compounds of the invention exist in stereoisomeric forms. The invention includes all stereoisomeric forms of the compounds including enantiomers and diastereomers. An example of enantiomers is shown below. Methods of making and separating stereoisomers are known in the art.



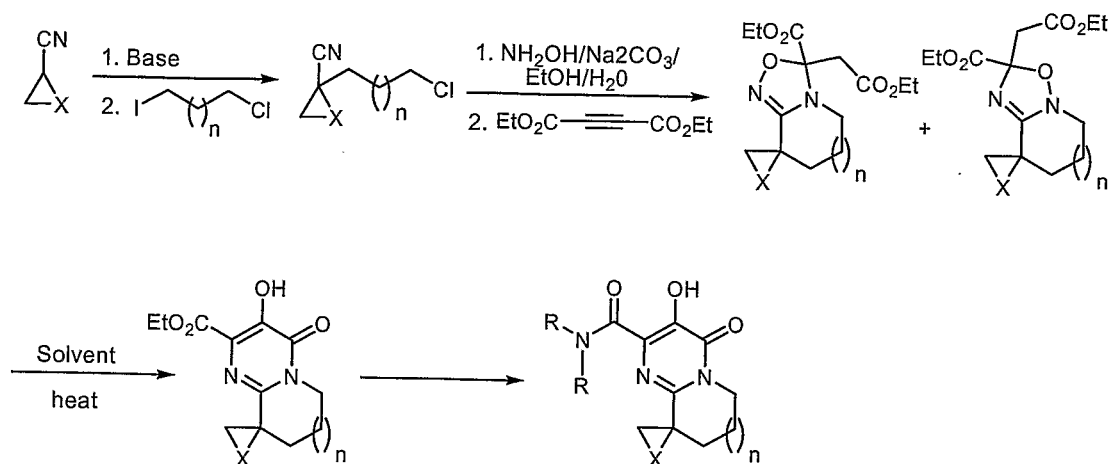
10

Synthetic Methods

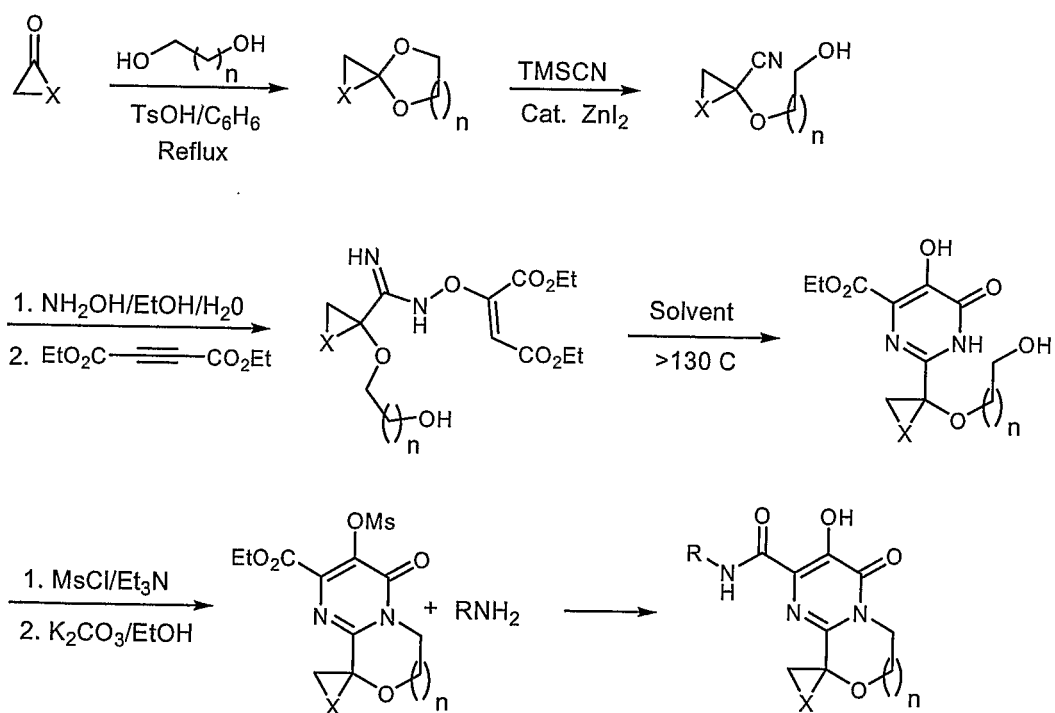
The compounds of this invention can be made by various methods known in the art including those of the following schemes and in the specific embodiments section. The variables shown in the schemes (for example, X, n, and P) are separate from and should not be confused with the variables in the claims or the rest of the specification. The variables in the schemes are meant only to illustrate how to make some of the compounds of this invention. "X" and "n" include alkylene spacers which may contain ether or amino functionalities. "P" may include an appropriate protecting group. Starting materials can be made using methods known in the art.

20

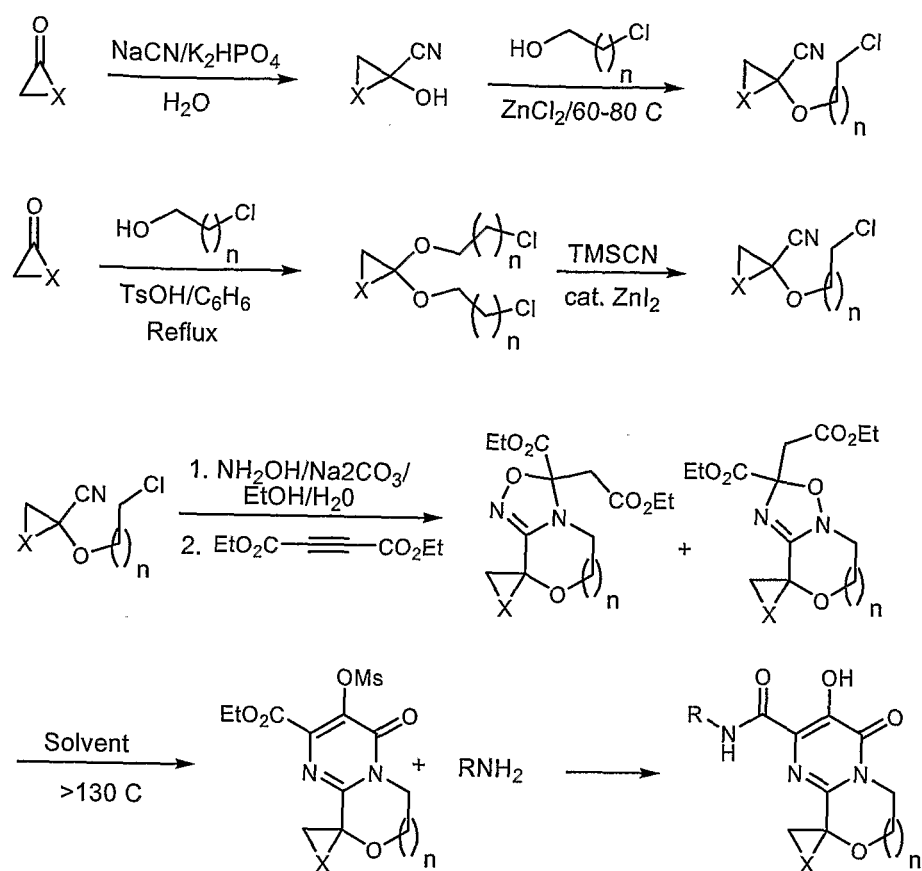
Scheme 1.



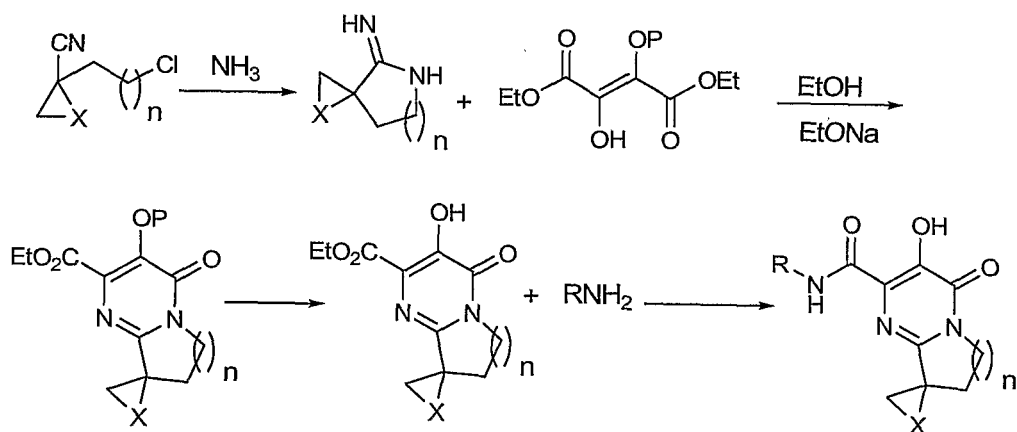
5 Scheme 2.



Scheme 3.



5 Scheme 4.



Biological Methods

To evaluate *in-vitro* activity against HIV-integrase, 5 pmole of biotin labeled substrate DNA was bound to 100 µg of Streptavidin coated PVT SPA beads (Amersham Pharmacia Biotech). Recombinant integrase (0.26 ng) was incubated with the beads for 90 min at 37 °C. Unbound enzyme was removed by washing the complex followed by addition of inhibitors and 0.1 fmol of P33 labeled target DNA. The reaction was stopped by adding EDTA to a final concentration of 10 mM. Samples were counted in TopCountNXT (Packard) and the CPM was used as a measure of integration. The reaction condition was as described in Engelman, A. and Craigie, R. *J. Virol.* **1995**, 69, 5908. The sequences of substrate and target DNA were described in *Nucleic Acid Research* **1994**, 22,1121. Using this assay, the compounds of this invention were found to have an IC₅₀ from less than 0.1 µM (see Table 1).

Table 1. HIV Integrase Inhibition

Example	IC ₅₀
1	A
2	A
3	A
4	A
5	A
6	A
7	A
8	B
9	A
10	A
11	A
12	A
13	A
14	A
15	A
16	A
17	A
18	A
19	B
20	A
21	A
22	B
23	B

Example	IC ₅₀
24	B
25	B
26	B
27	A
28	A
29	A
30	B
31	B
32	A
33	A
34	A
35	B
36	A
37	A
38	A
39	A
40	A
41	A
42	A
43	B
44	A
45	A
46	B
47	B
48	A
49	A
50	A
51	A
52	A
53	A
54	A
55	A
56	B
57	A
58	B
59	A
60	A
61	B
62	A
63	B
64	B
65	A
66	A
67	A
68	B
69	A

Example	IC ₅₀
70	A
71	B
72	A
73	A
74	B
75	B
76	A
77	A
78	A
79	A
80	A
81	A
82	A
83	B
84	A
85	A
86	B
87	A
88	B
89	A
90	B
91	A

Activity. A: 0.001-0.01 μ M; B: 0.01-0.1 μ M.

Pharmaceutical Composition and Methods of Use

5 The compounds of this invention inhibit HIV integrase. HIV integrase inhibitors have been reported to prevent viral integration and inhibited HIV-1 replication in cells (Hazuda et al. *Science* **2000**, 287, 646). Recently, HIV integrase inhibitors have been accepted into clinical trials for treating AIDS and HIV infection (Neamati *Expert. Opin. Ther. Patents* **2002**, 12, 709, Pais and Burke *Drugs Fut.* **2002**, 27, 1101).

10 Accordingly, another aspect of the invention is a method for treating HIV infection in a patient comprising administering a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof, with a pharmaceutically acceptable carrier.

Another aspect of the invention is a method for treating HIV infection in a patient comprising administering a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof, with a therapeutically effective amount of at least one other agent used for treatment of
5 AIDS or HIV infection. Some suitable agents are nucleoside HIV reverse transcriptase inhibitors, non-nucleoside HIV reverse transcriptase inhibitors, HIV protease inhibitors, HIV fusion inhibitors, HIV attachment inhibitors, CCR5 inhibitors, CXCR4 inhibitors, HIV budding or maturation inhibitors, and HIV integrase inhibitors.

10

Another aspect of the invention is a composition comprising a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof, with a pharmaceutically acceptable carrier.

15 “Combination,” “coadministration,” “concurrent,” and similar terms referring to the administration of compounds of Formula I with at least one anti-HIV agent mean that the components are part of a combination antiretroviral therapy or highly active antiretroviral therapy (HAART) as understood by practitioners in the field of AIDS and HIV infection.

20

“Therapeutically effective” means the amount of agent required to provide a meaningful patient benefit as understood by practitioners in the field of AIDS and HIV infection. In general, the goals of treatment are suppression of viral load, restoration and preservation of immunologic function, improved quality of life, and
25 reduction of HIV-related morbidity and mortality.

“Patient” means a person infected with the HIV virus and suitable for therapy as understood by practitioners in the field of AIDS and HIV infection.

30 “Treatment,” “therapy,” “regimen,” “HIV infection,” “ARC,” “AIDS” and related terms are used as understood by practitioners in the field of AIDS and HIV infection.

The compounds of this invention are generally given as pharmaceutical compositions comprised of a therapeutically effective amount of a compound of Formula I or its pharmaceutically acceptable salt and a pharmaceutically acceptable carrier and may contain conventional excipients. A therapeutically effective amount is that which is needed to provide a meaningful patient benefit. Pharmaceutically acceptable carriers are those conventionally known carriers having acceptable safety profiles. Compositions encompass all common solid and liquid forms including capsules, tablets, lozenges, and powders as well as liquid suspensions, syrups, elixers, and solutions. Compositions are made using common formulation techniques, and conventional excipients (such as binding and wetting agents) and vehicles (such as water and alcohols) are generally used for compositions.

Solid compositions are normally formulated in dosage units and compositions providing from about 1 to 1000 mg of the active ingredient per dose are preferred. Some examples of dosages are 1 mg, 10 mg, 100 mg, 250 mg, 500 mg, and 1000 mg. Generally, other antiretroviral agents will be present in a unit range similar to agents of that class used clinically. Typically, this is 0.25-1000 mg/unit.

Liquid compositions are usually in dosage unit ranges. Generally, the liquid composition will be in a unit dosage range of 1-100 mg/mL. Some examples of dosages are 1 mg/mL, 10 mg/mL, 25 mg/mL, 50 mg/mL, and 100 mg/mL. Generally, other antiretroviral agents will be present in a unit range similar to agents of that class used clinically. Typically, this is 1-100 mg/mL.

The invention encompasses all conventional modes of administration; oral and parenteral methods are preferred. Generally, the dosing regimen will be similar to other antiretroviral agents used clinically. Typically, the daily dose will be 1-100 mg/kg body weight daily. Generally, more compound is required orally and less parenterally. The specific dosing regime, however, will be determined by a physician using sound medical judgment.

The invention also encompasses methods where the compound is given in combination therapy. That is, the compound can be used in conjunction with other

agents useful in treating AIDS and HIV infection. Some of these agents include HIV attachment inhibitors, CCR5 inhibitors, CXCR4 inhibitors, HIV cell fusion inhibitors, HIV integrase inhibitors, HIV nucleoside reverse transcriptase inhibitors, HIV non-nucleoside reverse transcriptase inhibitors, HIV protease inhibitors, budding and maturation inhibitors, immunomodulators, and anti-infectives. In these combination methods, the compound will generally be given in a daily dose of 1-100 mg/kg body weight daily in conjunction with other agents. The other agents generally will be given in the amounts used therapeutically. The specific dosing regime, however, will be determined by a physician using sound medical judgment.

10

Table 2 lists some agents useful in treating AIDS and HIV infection which are suitable for this method.

Table 2. ANTIVIRALS

DRUG NAME	MANUFACTURER	INDICATION
097 (non-nucleoside reverse transcriptase inhibitor)	Hoechst/Bayer	HIV infection, AIDS, ARC
Amprenavir 141 W94 GW 141 (protease inhibitor)	Glaxo Wellcome	HIV infection, AIDS, ARC
Abacavir (1592U89) GW 1592 (RT inhibitor)	Glaxo Wellcome	HIV infection, AIDS, ARC
Acemannan	Carrington Labs (Irving, TX)	ARC
Acyclovir	Burroughs Wellcome	HIV infection, AIDS, ARC, in combination with AZT
AD-439	Tanox Biosystems	HIV infection, AIDS, ARC
AD-519	Tanox Biosystems	HIV infection, AIDS, ARC
Adefovir dipivoxil AL-721	Gilead Sciences Ethigen (Los Angeles, CA)	HIV infection, ARC, PGL HIV positive, AIDS
Alpha Interferon HIV in combination w/Retrovir	Glaxo Wellcome	Kaposi's sarcoma

DRUG NAME	MANUFACTURER	INDICATION
Ansamycin LM 427	Adria Laboratories (Dublin, OH) Erbamont (Stamford, CT)	ARC
Antibody which Neutralizes pH Labile alpha aberrant Interferon	Advanced Biotherapy Concepts (Rockville, MD)	AIDS, ARC
AR177	Aronex Pharm	HIV infection, AIDS, ARC
Beta-fluoro-ddA	Nat'l Cancer Institute	AIDS-associated diseases
BMS-232623 (CGP-73547) (protease inhibitor)	Bristol-Myers Squibb/ Novartis	HIV infection, AIDS, ARC
BMS-234475 (CGP-61755) (protease inhibitor)	Bristol-Myers Squibb/ Novartis	HIV infection, AIDS, ARC
CI-1012	Warner-Lambert	HIV-1 infection
Cidofovir	Gilead Science	CMV retinitis, herpes, papillomavirus
Curdlan sulfate	AJI Pharma USA	HIV infection
Cytomegalovirus Immune globin	MedImmune	CMV retinitis
Cytovene	Syntex	Sight threatening
Ganciclovir		CMV peripheral, CMV retinitis
Delaviridine (RT inhibitor)	Pharmacia-Upjohn	HIV infection, AIDS, ARC
Dextran Sulfate	Ueno Fine Chem. Ind. Ltd. (Osaka, Japan)	AIDS, ARC, HIV positive asymptomatic
ddC Dideoxycytidine	Hoffman-La Roche	HIV infection, AIDS, ARC
ddI Dideoxyinosine	Bristol-Myers Squibb	HIV infection, AIDS, ARC; combinationwith AZT/d4T
DMP-450 (protease inhibitor)	AVID (Camden, NJ)	HIV infection, AIDS, ARC

DRUG NAME	MANUFACTURER	INDICATION
Efavirenz (DMP 266) (-)-6-Chloro-4-(S)- cyclopropylethynyl- 4(S)-trifluoro- methyl-1,4-dihydro- 2H-3,1-benzoxazin- 2-one, STOCRINE (non-nucleoside RT inhibitor)	DuPont Merck	HIV infection, AIDS, ARC
EL10	Elan Corp, PLC (Gainesville, GA)	HIV infection
Famciclovir	Smith Kline	herpes zoster, herpes simplex
FTC (reverse transcriptase inhibitor)	Emory University	HIV infection, AIDS, ARC
GS 840 (reverse transcriptase inhibitor)	Gilead	HIV infection, AIDS, ARC
HBV097 (non-nucleoside reverse transcriptaseinhibitor)	Hoechst Marion Roussel	HIV infection, AIDS, ARC
Hypericin	VIMRx Pharm.	HIV infection, AIDS, ARC
Recombinant Human Interferon Beta	Triton Biosciences (Alameda, CA)	AIDS, Kaposi's sarcoma, ARC
Interferon alfa-n3	Interferon Sciences	ARC, AIDS
Indinavir	Merck	HIV infection, AIDS, ARC, asymptomatic HIV positive, also in combination with AZT/ddI/ddC
ISIS 2922	ISIS Pharmaceuticals	CMV retinitis
KNI-272	Nat'l Cancer Institute	HIV-associated diseases
Lamivudine, 3TC (reverse transcriptase inhibitor)	Glaxo Wellcome	HIV infection, AIDS, ARC, also with AZT
Lobucavir	Bristol-Myers Squibb	CMV infection
Nelfinavir (protease inhibitor)	Agouron Pharmaceuticals	HIV infection, AIDS, ARC
Nevirapine (RT inhibitor)	Boeheringer Ingelheim	HIV infection, AIDS, ARC
Novapren	Novaferon Labs, Inc. (Akron, OH)	HIV inhibitor

DRUG NAME	MANUFACTURER	INDICATION
Peptide T Octapeptide Sequence	Peninsula Labs (Belmont, CA)	AIDS
Trisodium Phosphonoformate	Astra Pharm. Products, Inc.	CMV retinitis, HIV infection, other CMV infections
PNU-140690 (protease inhibitor)	Pharmacia Upjohn	HIV infection, AIDS, ARC
Probucol	Vyrex	HIV infection, AIDS
RBC-CD4	Sheffield Med. Tech (Houston, TX)	HIV infection, AIDS, ARC
Ritonavir (protease inhibitor)	Abbott	HIV infection, AIDS, ARC
Saquinavir (protease inhibitor)	Hoffmann- LaRoche	HIV infection, AIDS, ARC
Stavudine; d4T Didehydrodeoxy- thymidine	Bristol-Myers Squibb	HIV infection, AIDS, ARC
Valaciclovir	Glaxo Wellcome	Genital HSV & CMV infections
Virazole Ribavirin	Viratek/ICN (Costa Mesa, CA)	asymptomatic HIV- positive, LAS, ARC
VX-478	Vertex	HIV infection, AIDS, ARC
Zalcitabine	Hoffmann-LaRoche	HIV infection, AIDS, ARC, with AZT
Zidovudine; AZT	Glaxo Wellcome	HIV infection, AIDS, ARC, Kaposi's sarcoma, in combination with other therapies
Tenofovir disoproxil, fumarate salt (Viread®) (reverse transcriptase inhibitor)	Gilead	HIV infection, AIDS
Combivir® (reverse transcriptase inhibitor)	GSK	HIV infection, AIDS
abacavir succinate (or Ziagen®) (reverse transcriptase inhibitor)	GSK	HIV infection, AIDS
Reyataz® (atazanavir)	Bristol-Myers Squibb	HIV infection, AIDS
Fuzeon (Enfuvirtide, T-20)	Roche/Trimeris	HIV infection, AIDS, viral fusion inhibitor
Trizivir®		HIV infection, AIDS

DRUG NAME	MANUFACTURER	INDICATION
Kaletra®	Abbott	HIV infection, AIDS, ARC

IMMUNOMODULATORS

DRUG NAME	MANUFACTURER	INDICATION
AS-101	Wyeth-Ayerst	AIDS
Bropirimine	Pharmacia Upjohn	Advanced AIDS
Acemannan	Carrington Labs, Inc. (Irving, TX)	AIDS, ARC
CL246,738	American Cyanamid Lederle Labs	AIDS, Kaposi's sarcoma
EL10	Elan Corp, PLC (Gainesville, GA)	HIV infection
FP-21399	Fuki ImmunoPharm	Blocks HIV fusion with CD4+ cells
Gamma Interferon	Genentech	ARC, in combination w/TNF (tumor necrosis factor)
Granulocyte Macrophage Colony Stimulating Factor	Genetics Institute Sandoz	AIDS
Granulocyte Macrophage Colony Stimulating Factor	Hoechst-Roussel Immunex	AIDS
Granulocyte Macrophage Colony Stimulating Factor	Schering-Plough	AIDS, combination w/AZT
HIV Core Particle Immunostimulant	Rorer	Seropositive HIV
IL-2 Interleukin-2	Cetus	AIDS, in combination w/AZT
IL-2 Interleukin-2	Hoffman-LaRoche Immunex	AIDS, ARC, HIV, in combination w/AZT
IL-2 Interleukin-2 (aldeslukin)	Chiron	AIDS, increase in CD4 cell counts
Immune Globulin Intravenous (human)	Cutter Biological (Berkeley, CA)	Pediatric AIDS, in combination w/AZT
IMREG-1	Imreg (New Orleans, LA)	AIDS, Kaposi's sarcoma, ARC, PGL
IMREG-2	Imreg (New Orleans, LA)	AIDS, Kaposi's sarcoma, ARC, PGL

DRUG NAME	MANUFACTURER	INDICATION
Imuthiol Diethyl Dithio Carbamate	Merieux Institute	AIDS, ARC
Alpha-2 Interferon	Schering Plough	Kaposi's sarcoma w/AZT, AIDS
Methionine- Enkephalin	TNI Pharmaceutical (Chicago, IL)	AIDS, ARC
MTP-PE Muramyl-Tripeptide Granulocyte Colony Stimulating Factor	Ciba-Geigy Corp. Amgen	Kaposi's sarcoma AIDS, in combination w/AZT
Remune	Immune Response Corp.	Immunotherapeutic
rCD4 Recombinant Soluble Human CD4	Genentech	AIDS, ARC
rCD4-IgG hybrids		AIDS, ARC
Recombinant Soluble Human CD4	Biogen	AIDS, ARC
Interferon Alfa 2a	Hoffman-La Roche in combination w/AZT	Kaposi's sarcoma, AIDS, ARC
SK&F106528 Soluble T4	Smith Kline	HIV infection
Thymopentin	Immunobiology Research Institute (Annandale, NJ)	HIV infection
Tumor Necrosis Factor; TNF	Genentech	ARC, in combination w/gamma Interferon

ANTI-INFECTIVES

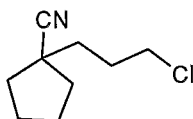
DRUG NAME	MANUFACTURER	INDICATION
Clindamycin with Primaquine	Pharmacia Upjohn	PCP
Fluconazole	Pfizer	Cryptococcal meningitis, candidiasis
Pastille Nystatin Pastille	Squibb Corp.	Prevention of oral candidiasis
Ornidyl Eflornithine	Merrell Dow	PCP
Pentamidine Isethionate (IM & IV)	LyphoMed (Rosemont, IL)	PCP treatment
Trimethoprim		Antibacterial
Trimethoprim/sulfa		Antibacterial
Piritrexim	Burroughs Wellcome	PCP treatment

DRUG NAME	MANUFACTURER	INDICATION
Pentamidine Isethionate for Inhalation	Fisons Corporation	PCP prophylaxis
Spiramycin	Rhone-Poulenc diarrhea	Cryptosporidial
Intraconazole-R51211	Janssen-Pharm.	Histoplasmosis; cryptococcal meningitis
Trimetrexate	Warner-Lambert	PCP
Daunorubicin	NeXstar, Sequus	Kaposi's sarcoma
Recombinant Human Erythropoietin	Ortho Pharm. Corp.	Severe anemia assoc. with AZT therapy
Recombinant Human Growth Hormone	Serono	AIDS-related wasting, cachexia
Megestrol Acetate	Bristol-Myers Squibb	Treatment of anorexia assoc. W/AIDS
Testosterone	Alza, Smith Kline	AIDS-related wasting
Total Enteral Nutrition	Norwich Eaton Pharmaceuticals	Diarrhea and malabsorption related to AIDS

DESCRIPTION OF SPECIFIC EMBODIMENTS

5

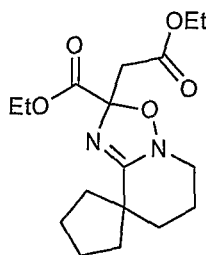
Intermediate 1



1-(3-chloropropyl)cyclopentanecarbonitrile. To a stirred solution of cyclopentanecarbonitrile (1.04 mL, 10 mmol) in THF (20 mL) at -78 °C was added
 10 LiHMDS (1M in THF, 11 mL) via syringe. After 30 min, 1-chloro-3-iodopropane (1.6 mL, 15 mmol) was added at once and slowly warmed to room temperature. After 20 h, the reaction mixture was quenched with saturated ammonium chloride (1 mL), diluted with EtOAc (100 mL), dried (MgSO₄), filtered and concentrated to give
 15 intermediate 1 as yellow oil which was used in the next step without further purification.

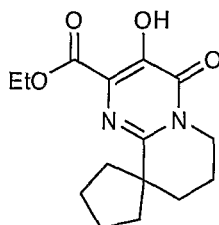
33

Intermediate 2



To a stirred mixture of intermediate 1 from previous experiment and
5 hydroxylamine hydrochloride (1.39 g, 20 mmol) in 1:1 EtOH/water (30 mL) was
added sodium carbonate (1.6 g, 15 mmol) over 5 min. Then, the reaction mixture
was stirred to 80 °C for 15 h and concentrated to dryness. The resulting white
residue was re-dissolved into 1:1 EtOH/water (30 mL) and diethyl
acetylenedicarboxylate (2.4 mL, 15 mmol) was added. After 1h, the reaction mixture
10 was diluted with water (50 mL) and extracted with EtOAc (3 X 50 mL). The
combined EtOAc extracts dried (Na₂SO₄), filtered and concentrated to give brown
oil. Flash chromatography using 9:1, 4:1 and 7:1 Hexanes/EtOAc mixtures afforded
intermediate 2 as pale yellow oil (1.03 g, 30%). ¹H NMR (500 MHz, CDCl₃) δ: 4.34-
4.11 (4H, m), 3.50-3.46 (1H, m), 3.38-3.34 (1H, m), 3.31 (1H, d, J = 16.2 Hz), 2.91
15 (1H, d, J = 16.2 Hz), 2.23-2.13 (2H, m), 1.95-1.89 (2H, m), 1.74-1.69 (2H, m), 1.62
(2H, t, J = 5.9 Hz), 1.54-1.48 (2H, m), 1.34-1.23 (8H, m). HRMS (M+H) calcd for
C₁₇H₂₇N₂O₅: 339.1920; found: 339.1923.

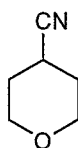
Intermediate 3



20

A solution of intermediate 2 (1.0 g, 2.955 mmol) in 3, 4-dichlorotoluene (10
mL) was heated at 210 °C for 15 h. Then, the reaction mixture was concentrated
under vacuum and the residue was purified by preparative HPLC using MeOH/water

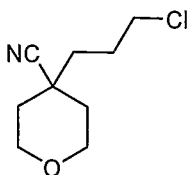
containing 0.1% TFA (gradient elution). The fractions containing the product were combined and concentrated to afford intermediate **3** as a dark paste (0.8639 g, 28.6%). ¹H NMR (500 MHz, CDCl₃) δ: 10.75 (1H, br s), 4.43 (2H, q, J = 7.0 Hz), 4.03 (2H, t, J = 5.8 Hz), 2.25-2.20 (2H, m), 1.99-1.93 (4H, m), 1.79-1.64 (6H, m), 1.42 (3H, t, J = 7.0 Hz), . HRMS (M+H) calcd for C₁₅H₂₁N₂O₄: 293.1501; found: 293.1513.

Intermediate **4**

10

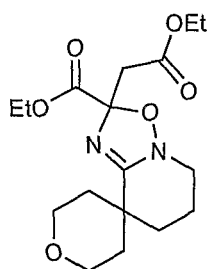
Tetrahydro-2H-pyran-4-carbonitrile. A solution of tetrahydro-4H-pyran-4-one (25 g, 250 mmol) and toluenesulfonylmethyl cyanide (53.7 g, 275 mmol) dissolved in ethylene glycol dimethylether (1 L) was cooled to 0 °C. Added dropwise over 30 min was a solution of potassium t-butoxide (56 g, 500 mmol) dissolved in t-butanol (350 mL) and ethylene glycol dimethylether (150 mL). After stirring the resulting mixture for 3 h at room temp, diethyl ether (1 L) was added and the organic phase was washed with saturated aqueous NaHCO₃. The organic phase was dried (Na₂SO₄) and concentrated. The residue was distilled at 39 °C 1.7 mm Hg to give the title compound as a colorless oil (10.87 g, 39% yield). ¹H NMR (300 MHz, CDCl₃) δ: 3.91-3.83 (2H, m), 3.61-3.54 (2H, m), 2.89-2.80 (1H, m), 1.97-1.78 (4H, m).

20

Intermediate **5**

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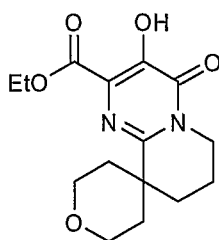
4-(3-chloropropyl)-tetrahydro-2H-pyran-4-carbonitrile. To a stirred solution of 1 M LiHMDS (25 mL, 25 mmol) in THF (10 mL) at -78 °C was added dropwise a solution of intermediate **4** (2.23 g, 20 mmol) in THF (15 mL) over 10 minutes. After 40 min, 1-chloro-3-iodopropane (2.7 mL, 25 mmol) was added at once, stirred at -78 °C for 1 h and 4 h room temperature. Then the reaction mixture was diluted with ether (100 mL), washed with water (20 mL) and brine (20 mL), dried (Na₂SO₄), filtered and concentrated to give yellow oil which was purified by flash column chromatography using 10-30% EtOAc/Hexanes to afford the product intermediate **5** as a colorless liquid (3.737 g, 99%). ¹H NMR (500 MHz, CDCl₃) δ: 3.97 (2H, dd, J = 11.3, 3.7 Hz), 3.71 (2H, td, J = 12.2, 1.8 Hz), 3.61 (2H, t, J = 6.3 Hz), 2.05-1.98 (2H, m), 1.88 (2H, dd, J = 13.4, 1.8 Hz), 1.77-1.74 (2H, m), 1.65-1.59 (2H, m).

Intermediate **6**

A mixture of intermediate **5** (1.83 g, 9.75 mmol) and NaI (3.0 g, 20 mmol) was stirred at ambient temperature for 1h. To this reaction mixture was added 50% aqueous hydroxylamine (1 mL, 10.87 mmol) and stirred for three-days at ambient temperature. To this was added diethyl acetylenedicarboxylate (1.6 mL, 10 mmol) and stirred for 1 h. Then, the reaction mixture was diluted with EtOAc (100 mL) washed with water (50 mL), brine (10 mL), dried (Na₂SO₄), filtered and concentrated to give yellow oil. Flash chromatography using 10-50% EtOAc/Hexanes afforded the desired intermediate **6** as pale yellow oil (0.627 g, 18%). ¹H NMR (500 MHz, CDCl₃) δ: . HRMS (M+H) calcd for C₁₇H₂₇N₂O₅;: found. ¹H NMR (500 MHz, CDCl₃) δ: 4.32-4.20 (2H, m), 4.14 (2H, q, J = 7.0 Hz), 3.86 (1H, td, J = 11.0, 2.7 Hz), 3.79-3.70 (3H, m), 3.52-3.46 (1H, m), 3.38-3.34 (1H,

m), 3.26 (1H, d, $J_{AB} = 16.2$ Hz), 2.97 (1H, d, $J_{AB} = 16.2$ Hz), 2.06-1.89 (4H, m), 1.66-1.66 (2H, m), 1.60-1.53 (2H, m), 1.30 (3H, t, $J = 7.0$ Hz), 1.24 (3H, t, $J = 7.0$ Hz).

Intermediate 7

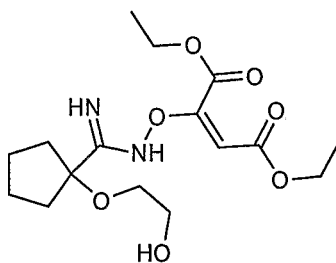


5

A solution of intermediate 6 (1.0 g, 2.955 mmol) in cyclohexylbenzene (25 mL) was heated at 200 °C for 15 h. Then, the reaction mixture was concentrated under vacuum and the residue was purified by preparative HPLC using MeOH/water containing 0.1% TFA (gradient elution). The fractions containing the product were combined and concentrated to afford intermediate 7 as an off-white solid (0.1263 g, 23%). ^1H NMR (500 MHz, CDCl_3) δ : 10.35 (1H, br s), 4.45 (2H, q, $J = 7.0$ Hz), 4.09-4.05 (2H, m), 4.01-3.99 (2H, m), 3.74-3.69 (2H, m), 2.35-2.29 (2H, m), 2.02-1.93 (4H, m), 1.59-1.54 (2H, m), 1.44 (3H, t, $J = 7.0$ Hz). HRMS ($\text{M}+\text{H}$) calcd for $\text{C}_{15}\text{H}_{21}\text{N}_2\text{O}_4$: 309.1451; found: 309.1463.

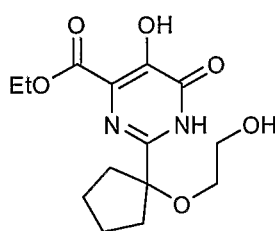
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Intermediate 8



20 *(E)*-2- $\{[1-(2\text{-Hydroxyethoxy})\text{cyclopentanecarboximidoyl}]\text{-aminoxy}\}$ but-2-enedioic acid diethyl ester. A stirred mixture of cyclopentanone ethylene ketal (12.82 g, 100 mmol) and ZnI_2 (45 mg, catalytic) was placed in water bath and to this was added trimethylsilyl cyanide (13.35 mL, 100 mmol) via syringe over 10 min.

After 16 h, EtOH (100 mL) followed by 50% aqueous hydroxylamine (6.43 mL, 100 mmol) was added and stirred at 80 °C for 2 h. Then, the reaction mixture was cooled in ice-water bath and diethyl acetylenedicarboxylate (16 mL, 100 mmol) was added over 5 min. Then, cooled bath removed, stirred for 4 h at room temperature and concentrated to give intermediate **8** as a dark-brown oil which was used in the next step without purification. LRMS (M+H) calcd for C₁₆H₂₇N₂O₇: 359.2; found: 359.2.

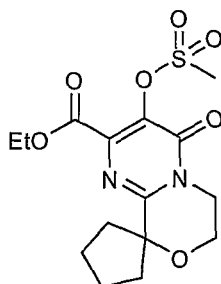
Intermediate **9**

10

5-Hydroxy-2-[3-(2-hydroxy-ethoxy)tetrahydrofuran-3-yl]-6-oxo-1,6-dihydropyrimidine-4-carboxylic acid ethyl ester. A xylenes (200 ml) solution of crude intermediate **8** (100 mmol) was heated at reflux for 24 h, cooled and concentrated. The resulting dark-residue was stirred with 0.5 M Na₂CO₃ (150 mL) for 30 min and extracted with EtOAc (3 X 50 mL). The combined organic phases were re-extracted with 0.5 M Na₂CO₃ (50 mL) and EtOAc extracts discarded. The combined aqueous layers was carefully acidified with conc. HCl (20 mL) and extracted with CH₂Cl₂ (4 X 50 mL). The combined CH₂Cl₂ layers dried (Na₂SO₄/activated charcoal), filtered and concentrated to give brown solid which triturated with ether and filtered to afford intermediate **9** as a light brown powder (11.81 g, 38%). This material is contaminated with about 15% of an identified impurity whose M+1 = 295. LRMS (M+H) calcd for C₁₄H₂₁N₂O₆: 313.32; found: 313.27.

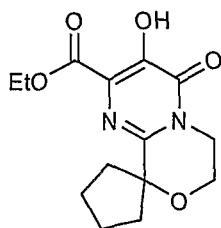
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Intermediate 10



To a stirred solution of crude intermediate **9** (11.67 g) in THF (100 mL) at
 5 °C was added MsCl (8.7 mL, 112.4 mmol) followed by Et₃N (15.8 mL, 112.5
 mmol). The resulting turbid reaction mixture was stirred for 4 h while allowing it to
 warm to room temperature. Then diluted with EtOAc (200 mL), washed with water
 (2 X 50 mL), brine (50 mL), dried (Na₂SO₄), filtered and concentrated to give
 viscous yellow oil. This oil was re-dissolved in anhydrous EtOH (100 mL) and
 10 stirred with K₂CO₃ (4.15 g, 30 mmol). After 4 h, the viscous slurry was diluted with
 EtOAc (150 mL) and continued stirring for additional 1 h. Then, the reaction
 mixture was filtered and concentrated to give white solid which was triturated with
 ether, and filtered to afford intermediate **10** as a white fluffy solid (8.284 g, 64%). ¹H
 NMR (500 MHz, CDCl₃) δ: 4.43 (2H, q, J = 7.0 Hz), 3.99 (4H, s), 3.53 (3H, s), 2.33-
 15 2.28 (2H, m), 2.09-2.05 (2H, m), 1.93-1.82 (4H, m), 1.40 (3H, t, J = 7.0 Hz). HRMS
 (M+H) calcd for C₁₅H₂₁N₂O₇S: 373.1069; found: 373.1053.

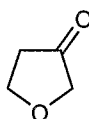
Intermediate 11



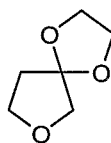
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To a stirred suspension of intermediate **10** (0.6861 g, 1.84 mmol) in THF (50
 mL) was added 1M EtONa/EtOH (10 mL). After 1h, the resulting yellow solution
 was concentrated, acidified with 1 M aq. HCl (20 mL), extracted with CH₂Cl₂ (3 X

35 mL). The combined organic layers dried (Na₂SO₄), filtered and concentrated to give intermediate **11** as a brown solid (0.4668 g, 86%). ¹H NMR (500 MHz, CDCl₃) δ: 10.49 (1H, s), 4.44 (2H, q, J = 7.0 Hz), 4.03-3.97 (4H, m), 2.28-2.22 (2H, m), 2.06-2.01 (2H, m), 1.93-1.81 (4H, m), 1.42 (3H, t, J = 7.0 Hz). HRMS (M+H) calcd for C₁₄H₁₉N₂O₅: 295.1294; found: 295.1293.

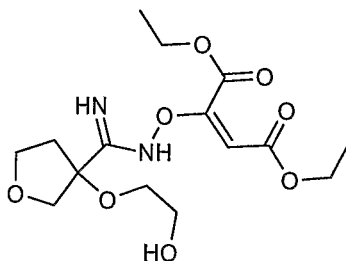
Intermediate **12**

10 *Dihydrofuran-3(2H)-one*. A mixture of 3-hydroxyfuran (24 g, 272 mmol) and TEMPO (0.86 g, 5.5 mmol) in CH₂Cl₂ (175 mL) and KBr (7.141 g, 60 mmol) in water was vigorously stirred and cooled in an ice-water bath. The pH of NaOCl (commercial grade bleach, 600 mL, 806 mmol) was adjusted to 9.5 by dissolving NaHCO₃ (8.632 g, 102.75 mmol) immediately before use. This NaOCl solution was
15 added over 40 min while keeping the internal temperature of the reaction mixture between 0 °C and 5 °C. After 2 h, the greenish-yellow organic phase was separated and aqueous phase was saturated with NaCl and extracted with CH₂Cl₂ (4 X 100 mL). The combined organic phases was washed with 10% HCl aq. (1 X 300 mL) containing KI (12 g) and 10% aq. Na₂CO₃ (2 X 150 mL). The organic layer dried
20 (Na₂SO₄), filtered and concentrated to give intermediate **12** as a pale yellow liquid (15.79 g, 67%) which was used without purification. ¹H NMR (500 MHz, CDCl₃) δ: 4.24 (2H, t, J = 7.3 Hz), 3.86 (2H, s), 2.49 (2H, t, J = 7.3 Hz).

Intermediate **13**

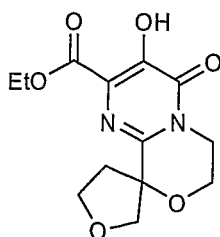
1,4,7-Trioxaspiro[4.4]nonane. A mixture of intermediate **12** (15.79 g, 183.5 mmol), ethylene glycol (16.7 mL, 300 mmol) and cat. TsOH•H₂O (100 mg) in benzene (100 mL) was heated at reflux using Dean-Stark trap. After 17 h, the reaction mixture was cooled, diluted with ether (150 mL), washed with sat. Na₂CO₃ and brine (50 mL each), dried (Na₂SO₄), filtered and concentrated to give yellow liquid. Distillation under reduced pressure afforded intermediate **13** as a yellow liquid (19.13 g, 80%). ¹H NMR (500 MHz, CDCl₃) δ: 3.9.4 (2H, t, J = 7.0 Hz), 3.94-3.90 (4H, m), 3.68 (2H, s), 2.09 (2H, t, J = 7.0 Hz).

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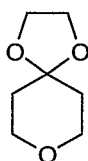
Intermediate **14**

(E)-2-[[3-(2-Hydroxy-ethoxy)tetrahydrofuran-3-carboximidoyl]-aminoxy]but-2-enedioic acid diethyl ester. Prepared according to the procedure for intermediate **8**. Yield: 38%; viscous yellow paste. ¹H NMR (500 MHz, CDCl₃) δ: 5.78 (1H, d, J = 7.6 Hz), 5.59 (1H, br s), 5.38 (1H, s), 4.37-4.27 (2H, m), 4.20-4.13 (2H, m), 4.03-3.87 (4H, m), 3.79-3.75 (2H, m), 3.53-3.45 (2H, m), 1.60 (1H, br s), 1.38-1.23 (6H, m). HRMS (M+H) calcd for C₁₅H₂₅N₂O₈: 361.1611; found: 361.1620.

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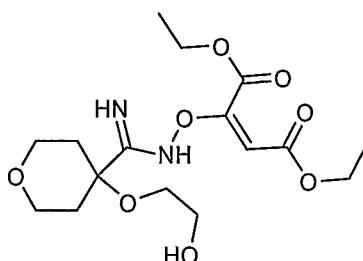
Intermediate **15**

Prepared according to the procedure for intermediate **11**. Yield: 29%; brown solid. ^1H NMR (500 MHz, CDCl_3) δ : 10.63 (1H, br s), 4.44 (2H, q, $J = 7.0$ Hz), 4.18-4.11 (4H, m), 4.08-4.01 (4H, m), 2.66-2.60 (1H, m), 2.35-2.30 (1H, m), 1.41 (3H, t, $J = 7.0$ Hz). HRMS ($\text{M}+\text{H}$) calcd for $\text{C}_{13}\text{H}_{17}\text{N}_2\text{O}_6$: 297.1087; found: 297.1071.

Intermediate **16**

1,4,8-Trioxa-spiro[4.5]decane. A mixture of tetrahydro-4-pyranone (10 g, 99.9 mmol), ethylene glycol (20 mL, 150 mmol) and catalytic toluene sulfonic acid was refluxed in benzene (120 mL) for 5 h. After cooling to room temp, the benzene layer was decanted from the dark oil in the bottom of the flask and was concentrated. The resulting oil was taken up in methylene chloride and shaken in a separatory funnel. The CH_2Cl_2 layer was decanted from the insoluble oil. The CH_2Cl_2 layer was concentrated to give the intermediate **16** as a pale yellow oil (11.62 g, 81% yield). ^1H -NMR (300 MHz, CDCl_3) δ : 3.91 (4H, s), 3.71 (4H, t, $J = 5.5$ Hz), 1.68 (4H, t, $J = 5.7$ Hz).

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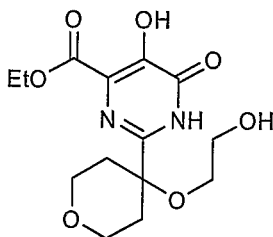
Intermediate **17**

(E)-2-[[4-(2-Hydroxyethoxy)tetrahydropyran-4-carboximidoyl]-aminoxy]but-2-enedioic acid diethyl ester. Prepared according to the procedure for intermediate **8**. Yield: 60%; yellow oil. ^1H -NMR (300 MHz, CDCl_3) δ : 5.72 (1H, d,

$J = 22.7$ Hz), 5.50 (1H, bs), 5.29 (1H, bs), 4.33-4.23 (2H, m), 4.19-4.04 (2H, m), 3.95-3.87 (1H, m), 3.79-3.63 (6H, m), 3.43-3.39 (2H, m), 2.15-1.74 (4H, m), 1.35-1.19 (6H, m). LCMS $[M+H]^+$ calcd for $C_{16}H_{27}N_2O_8$: 375.17; found: 375.19.

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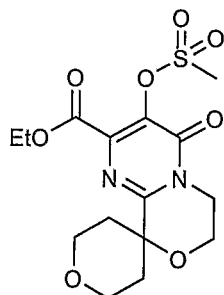
Intermediate 18



5-Hydroxy-2-[4-(2-hydroxyethoxy)tetrahydropyran-4-yl]-6-oxo-1,6-dihydropyrimidine-4-carboxylic acid ethyl ester. A solution of an intermediate 17 (9.3 g, 25 mmol) in xylenes (150 mL) was refluxed for 18 h. After cooling to room temp, the mixture was shaken with 0.2 M Na_2CO_3 . The aqueous phase was washed with EtOAc, made acidic with conc'd HCl and extracted with CH_2Cl_2 . The organic phase was dried (Na_2SO_4) and concentrated. The resulting residue was triturated with ether to give the intermediate 18 as a brown solid (0.87 g, 10% yield) and impure product (2.36 g). LCMS $[M+H]^+$ calcd for $C_{14}H_{21}N_2O_7$: 329.13; found: 329.15.

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Intermediate 19



A solution of intermediate 18 (0.86 g, 2.6 mmol) in THF (10 mL) was cooled to 0 °C. Added to this was methanesulfonyl chloride (0.613 mL, 7.9 mmol) followed

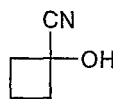
by slow addition of triethylamine (1.07 mL, 7.9 mmol). The mixture stirred for 4 h while gradually warming to room temp. before diluting with EtOAc. The mixture was washed with water and brine and dried (Na_2SO_4) before concentrating to give a dark oil. This was dissolved in EtOH (20 mL) and THF (10 mL) and added

5 potassium carbonate (0.56 g, 4.04 mmol). The mixture was stirred at room temp for 18 h, diluted with EtOAc (200 mL) and the solids were removed by filtration. The solution was concentrated and the residue was triturated with methanol. Filtration gave the intermediate **19** as a white solid (0.23 g, 23 %). ^1H -NMR (300 MHz, CDCl_3) δ : 4.41 (2H, q, $J = 7.2$ Hz), 4.03-3.98 (4H, m), 3.88-3.82 (2H, m), 3.74 (2H,

10 t, $J = 11.2$ Hz), 3.50 (3H, s), 2.44 (2H, dt, $J = 13.1, 4.9$ Hz), 1.76 (2H, d, $J = 13.9$ Hz), 1.38 (3H, t, $J = 7.1$ Hz). LCMS $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{15}\text{H}_{21}\text{N}_2\text{O}_8\text{S}_3$: 389.10; found: 389.13.

Intermediate **20**

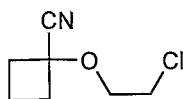
15



1-Hydroxycyclobutanecarbonitrile. To a flask containing cyclobutanone (13.41 g, 191 mmol) was added a solution of potassium phosphate monobasic (29.10 g, 214 mmol) in water (50 mL), followed by a solution of sodium cyanide (10.39 g,

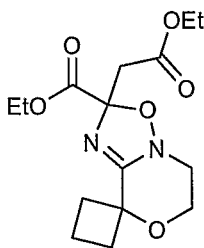
20 210 mmol) in water (50 mL), and the reaction was stirred for 16 hours. The reaction was treated with diethyl ether (100 mL) and stirred for 30 minutes. The separated aqueous layer was washed with ether (2 x 100 mL), and the combined extracts were concentrated to an oil. The oil was dissolved in dichloromethane, dried (sodium sulfate), filtered, and concentrated to give an amber oil (15.10 g), which contained

25 approximately 15% of intermediate **20**. The intermediate was used without further purification or treatment. ^1H NMR (500 MHz, CDCl_3) δ : 3.15 (1H, br s), 2.60 - 2.68 (2H, m), 2.29 - 2.38 (2H, m), 1.89 - 2.03 (2H, m).

Intermediate **21**

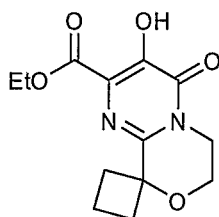
5 *1-(2-Chloroethoxy)cyclobutanecarbonitrile*. Zinc chloride (36.03 g, 264 mmol) was fused using a propane torch while under vacuum. The molten zinc was cooled and the evacuated flask was flushed with nitrogen. The flask was loaded with intermediate **2** (15.10 g,) and 2-chloroethanol (17.7 g, 218 mmol) and stirred with heating (90°C) for 20 hours. The reaction mixture was diluted with water (200 mL) and extracted with ethyl acetate (1 x 150 mL, 4 x 100 mL). The combined organic
10 layers were dried (sodium sulfate), filtered, and concentrated to an oil *in-vacuo*. The crude product was purified by vacuum distillation (b.p.₁₂ 85°C) to give intermediate **21** (5.00g, 31.3 mmol, 16.4% over two steps) as a clear liquid. ¹H NMR (500 MHz, CDCl₃) δ: 3.75 (2H, t, *J*=5.5 Hz), 3.65 (2H, t, *J*=5.6 Hz), 2.52 - 2.61 (2H, m), 2.31 - 2.43 (2H, m), 1.91 - 2.06 (2H, m).

15

Intermediate **22**

A solution of intermediate **21** (2.64 g, 16.5 mmol) in ethanol (10 mL) was
20 treated with a 50 weight-percent aqueous solution of hydroxylamine (3.34 g, 50 mmol), and stirred with heating (60 °C) for 16 hours. The solvent was removed *in vacuo*, and the residue was dried from ethanol-water (1:1, 10 mL) twice, to give as an oily solid. This was used immediately in the following step.

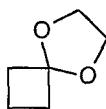
A cold (0 °C) solution of the above oily solid in ethanol (5 mL) and water (10 mL) was treated with a solution of diethyl acetylenedicarboxylate (4.22 g, 25 mmol) in ethanol (50 mL). The reaction was stirred for 5 minutes, then warmed to room temperature, and stirred for 2 hours. The reaction was diluted with water (50 mL) and extracted with ethyl acetate (3 x 50 mL). The combined extracts were dried (sodium sulfate), filtered, and concentrated *in vacuo*. The crude was partially purified by flash silica gel column chromatography, eluting with 10% to 35% ethyl acetate in hexanes. Product fractions were pooled and concentrated *in vacuo* to give intermediate **22** (2.58 g, 48%) as a yellow oil, which was used immediately in the following step. LC/MS $[M+H]^+ = 327.14$.

Intermediate **23**

A solution of intermediate **22** (2.51 g, 7.7 mmol) in 1,2,4-trimethyl benzene (25 mL) was heated at reflux (180 °C) for 3 hours, then cooled to room temperature. The solvent was removed *in vacuo*, and the crude was dissolved in ethyl acetate (75 mL) and extracted with a saturated aqueous solution of sodium bicarbonate (4 x 75 mL). The combined extracts were brought to pH 1-2 using 6N hydrochloric acid, and the resultant solid was extracted with ethyl acetate (4 x 50 mL). The combined extract was dried (sodium sulfate), filtered, and concentrated *in vacuo* to give intermediate **23** (0.235 g, 5.2% over two steps) as a brown solid. ^1H NMR (500 MHz, CDCl_3) δ : 10.54 (1H, s), 4.46 (2H, q, $J=7.1$ Hz), 3.95 - 4.00 (4H, m), 2.67 - 2.74 (2H, m), 2.30 (2H, ddd, $J=12.4, 9.9, 7.3$ Hz), 2.09 - 2.19 (1H, m), 1.97 - 2.06 (1H, m), 1.44 (3H, t, $J=7.2$ Hz). LC/MS $[M+H]^+ = 281.11$.

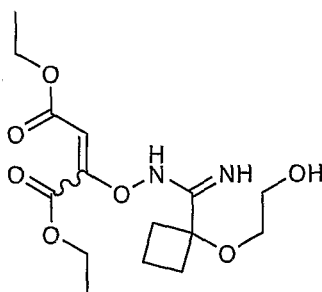
Alternative preparation of intermediate **23** from cyclobutanone.

Intermediate 24



5,8-Dioxa-spiro[3.4]octane. A solution of cyclobutanone (7.7 g, 0.11 mol),
 5 ethylene glycol (6.82 g, 0.11 mol) and p-toluenesulfonic acid mono hydrate (200 mg,
 1 mmol) in benzene (200 mL) was heated at reflux with a Dean-Stark trap for 14 hrs.
 After cooling, the mixture was washed with aqueous sodium bicarbonate solution
 (saturated, 15 mL), then with brine and dried (magnesium sulfate), filtered and
 concentrated to obtain 9.37 g (82%) of intermediate **24** as a colorless liquid: ^1H NMR
 10 (CDCl_3 , 500 MHz) δ ppm 3.87 (4H, s, CH_2), 2.31 (4H, t, $J = 8$ Hz, CH_2), 1.67 (2H, qt,
 $J = 8$ Hz, CH_2); ^{13}C NMR (CDCl_3 , 125.77 Hz) δ : 109.08 (C), 63.87 (CH_2), 35.58
 (CH_2), 11.42 (CH_2).

Intermediate 25



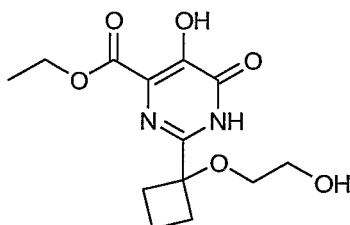
15

2-([1-(2-hydroxyethoxy)cyclobutanecarboximidoyl]-aminooxy)but-2-enedioic
 acid diethyl ester. To a mixture of intermediate **24** (5.70 g, 50 mmol) and
 trimethylsilyl cyanide (5.05 g, 50 mmol) was added a catalytic amount of ZnI_2 (12
 20 mg) in a cool water bath of $\sim 10^\circ\text{C}$ and the mixture stirred at room temperature for 5
 hrs to obtain 10.7 g of 1-(2-trimethylsilanyloxyethoxy)cyclobutanecarbonitrile as a
 mobile oil: ^1H NMR (CDCl_3 , 500 MHz) δ : 3.75 (2H, t, $J = 5$ Hz, OCH_2), 3.55 (2H, t,
 $J = 5$ Hz, OCH_2), 2.51-2.56 (2H, m, CH_2), 2.30-2.37 (2H, m, CH_2), 1.91-1.98 (2H, m,
 CH_2), 0.124 (9H, s, SiCH_3); ^{13}C NMR (CDCl_3 , 125.77 Hz) δ ppm 120.43 (CN), 72.05

(C), 67.71 (CH₂), 61.49 (CH₂), 34.02 (CH₂), 12.91 (CH₂), -0.29 (CH₃). LC/MS m/z 142 (M+H-SiMe₃).

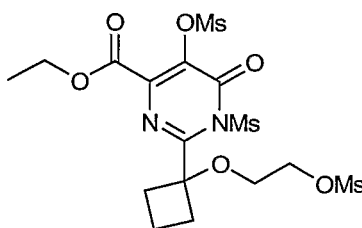
A solution of 1-(2-trimethylsilyloxyethoxy)cyclobutanecarbonitrile (3.5 g, 16.4 mmol) and 50 % aqueous hydroxylamine (1.08 g, 16.4 mmol) in EtOH (16 mL) was stirred in an oil bath heated at 80°C for 2.5 hrs and then cooled to room temperature. To a solution was added drop-wise diethyl acetylenedicarboxylate (2.93 g, 17.2 mmol) in an ice-bath and the mixture stirred at room temperature for 5 hrs. This mixture was concentrated in vacuo to obtain 6.16 g of a crude brownish oil containing intermediate **25**: ¹H NMR (500 MHz, CDCl₃) δ: 1.19-1.38 (6 H, m) 1.72-1.86 (2 H, m) 2.06-2.24 (2 H, m) 2.29-2.49 (2 H, m) 3.26-3.38 (2 H, m) 3.65-3.76 (2 H, m) 4.11-4.19 (2 H, m) 4.24-4.38 (2 H, m) 5.67 (0.25 H, s) 5.85 (0.5 H, s). HRMS (M+H) calcd for C₁₅H₂₅N₂O₇ 345.1662, found 345.1648.

15

Intermediate **26**

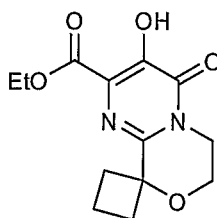
5-hydroxy-2-[1-(2-hydroxy-ethoxy)-cyclobutyl]-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid ethyl ester. A solution of a crude intermediate **25** (5.9 g) in xylenes (30 mL) was heated at 150-155 °C for 20 h. The mixture was concentrated in vacuo and the residue re-dissolved in EtOAc (30 mL) was extracted with 1M aq. sodium carbonate solution (3x20 mL). The aqueous extracts were acidified with careful addition of concentrated HCl, and this mixture was extracted with CH₂Cl₂ (2x20 mL). The combined organic extracts were dried (Na₂SO₄), filtered and concentrated to obtain intermediate **26** (1.19 g, 24% over three steps) as brownish oil: LC/MS m/z 299 (M+H).

Intermediate 27



5 *Ethyl 1-(methanesulfonyl)-5-(methanesulfonyloxy)-2-(1-(2-(methanesulfonyloxy)ethoxy)cyclobutyl)-6-oxo-1,6-dihydropyrimidine-4-carboxylate*
 (27): A cold (0°C) solution of intermediate 26 (7.23 g, 25 mmol) in anhydrous tetrahydrofuran was treated with methanesulfonylchloride (Aldrich) by dropwise addition. The solution was warmed to room temperature and stirred for 4 hrs. The
 10 reaction was concentrated in-vacuo, and the crude product was dissolved in ethyl acetate (75 mL) and washed with saturated sodium bicarbonate solution. The organic solution was dried (sodium sulfate), filtered to remove solids, and concentrated in vacuo to give intermediate 27 as a brown oil. This was used in the subsequent reaction without further purification. ¹H NMR (500 MHz, CDCl₃) δ: 4.49 (2H, q, *J* =
 15 7.0 Hz), 4.35-4.38 (2H, m), 3.93-4.00 (1H, m), 3.66-3.67 (3H, s), 3.62-3.65 (2H, m), 3.44-3.46 (3H, s), 3.05-3.07 (3H, s), 2.74-2.82 (1H, m), 2.60-2.67 (2H, m), 2.41-2.49 (2H, m), 1.43 (3H, t, *J* = 7.0 Hz). LCMS (M+H): 532.94.

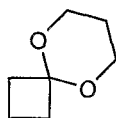
Intermediate 28



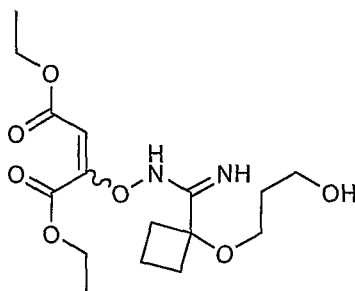
20 To a solution of intermediate 27 obtained above in absolute ethanol (50 mL) and anhydrous tetrahydrofuran (75 mL) was added anhydrous potassium carbonate (3.46 g, 25 mmol), and the reaction was stirred with heating (65°C) for 20 hrs. Solvent was removed in-vacuo and the crude product was dissolved in water (150

mL) and extracted with ethyl acetate (2 x 100 mL). The aqueous layer was made acidic (pH ~ 1-2) using 6.0 N hydrochloric acid, and the resulting solid was extracted with ethyl acetate (2 x 75 mL). The combined extract was dried (sodium sulfate), filtered to remove solids, and concentrated to give intermediate **28** (4.30 g, 61%) as a light brown solid. ¹H NMR (500 MHz, CDCl₃) δ: 10.57 (1H, s), 4.46 (2H, q, *J* = 7.2 Hz), 3.97 (4H, s), 2.67-2.73 (2H, m), 2.27-2.33 (2H, m), 2.10-2.18 (1H, m), 1.98-2.06 (1H, m), 1.44 (3H, t, *J* = 7.2 Hz). ¹³C NMR (126 MHz, CDCl₃) δ: 169.56, 157.68, 150.41, 148.19, 125.24, 79.09, 62.63, 58.52, 42.66, 34.72, 14.18, 13.87; LC/MS (M+H): 281.13.

10

Intermediate **29**

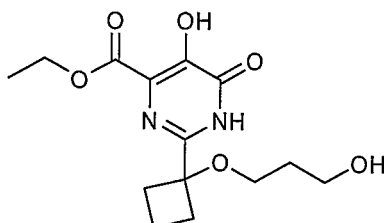
Intermediate **29** was prepared (50% yield) according to the procedure for intermediate **24**. ¹H NMR (500 MHz, C₆D₆) δ: 3.49 (4H, t, *J* = 5.5 Hz), 2.23 (4H, t, *J* = 8 Hz), 1.63 (2H, qt, *J* = 8 Hz), 1.24 (2H, qt, *J* = 5.5 Hz).

Intermediate **30**

20

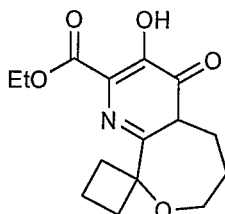
Intermediate **30** was prepared (52% yield) according to the procedure for intermediate **25**. ¹H NMR (500 MHz, C₆D₆) δ: 3.54 (2H, t, *J* = 6.1 Hz), 3.45 (2H, t, *J* = 6.1 Hz), 2.06 - 2.12 (2H, m), 1.87 (2H, dq, *J* = 9.7, 2.6 Hz), 1.68 (2H, qt, *J* = 6.1 Hz), 1.43 - 1.51 (1H, m), 1.26 - 1.34 (1H, m), 0.10 (9H, s). LC/MS [M+H]⁺ = 359.20

Intermediate 31



Intermediate 31 was prepared (69% yield) according to the procedure for intermediate 26. ^1H NMR (500 MHz, CDCl_3) δ : 4.46 (2H, q, $J=7.0$ Hz), 3.84 (2H, t, $J=5.5$ Hz), 3.41 (2H, t, $J=5.5$ Hz), 2.51 - 2.58 (2H, m), 2.29 - 2.38 (2H, m), 1.89 - 1.99 (2H, m), 1.82 - 1.90 (3H, m), 1.45 (3H, t, $J=7.0$ Hz), 1.31 - 1.41 (1H, m). LC/MS (ESI) $[\text{M}+\text{H}]^+ = 313.05$.

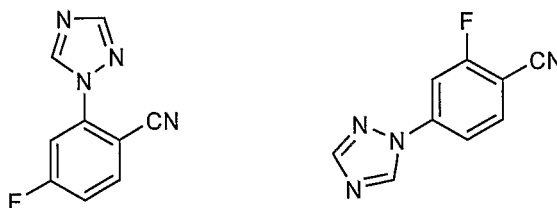
Intermediate 32



A cold (0°C) solution of intermediate 31 (3.0 g, 9.6 mmol) in tetrahydrofuran (25 mL) was treated with methanesulfonyl chloride (3.30 g, 29 mmol) followed by dropwise addition of triethylamine (4.7 mL, 33.6 mmol). The reaction was stirred for 16 hours at room temperature. The solvent was removed *in vacuo* and the mixture was dissolved in ethanol (50 mL) and dimethylformamide (25 mL). To the slurry was added potassium carbonate (1.36 g, 9.7 mmol) and the reaction was stirred at room temperature for 16 hours, followed by heating (80°C) for 3 hours. The solvent was removed *in vacuo*. The crude product was diluted with ethyl acetate (50 mL) and washed with 1N hydrochloric acid (2 x 50 mL), extracted with ethyl acetate (2 x 25 mL) then brine ((50 mL). The solution was then dried (sodium sulfate), filtered and concentrated to give intermediate 32 (0.534 g, 19%) as a brown solid. ^1H NMR

(500 MHz, CDCl₃) δ : 10.64 (1H, br s), 4.45 (2H, q, $J=7.0$ Hz), 4.38 (2H, br), 3.91 (2H, t, $J=5.0$ Hz), 2.81 (2H, br), 2.36 - 2.44 (2H, m), 1.87 - 1.97 (1H, m), 1.82 - 1.86 (2H, m), 1.67 - 1.75 (1H, m), 1.43 (3H, t, $J=7.2$ Hz).

5

Intermediates **33** and **34**

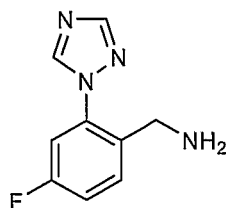
4-Fluoro-2-(1H-1,2,4-triazol-1-yl)benzonitrile (33) and 4-(1H-1,2,4-triazol-1-yl)-2-fluorobenzonitrile. To a solution of 2,4-difluorobenzonitrile (10 g, 72 mmol) dissolved in THF (20 mL), and DMF (40 mL) was added 1,2,4-triazole sodium derivative (6.3 g, 70 mmol) and the mixture was stirred at 90 °C for 3 h, filtered and concentrated. The residue was adsorbed onto Silica gel and purified by flash chromatography eluting with 0%-10%-30% EtOAc/hexanes to give intermediate **33** as colorless needles (2.46 g, 18%) and intermediate **34** was obtained as a white solid (0.7455 g, 6%).

20

Intermediate **33**: ¹H NMR (500 MHz, CDCl₃) δ : 8.89 (1H, s), 8.19 (1H, s), 7.85 (1H, dd, $J=8.7, 5.6$ Hz), 7.60 (1H, dd, $J=8.8, 2.4$ Hz), 7.28-7.24 (1H, m). LCMS (M+H) calcd for C₉H₆N₄F: 189.05; found: 189.13.

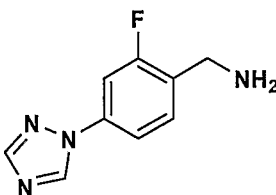
Intermediate **34**: ¹H NMR (500 MHz, CDCl₃) δ : 8.66 (1H, s), 8.15 (1H, s), 7.79 (1H, dd, $J=8.5, 6.7$ Hz), 7.69 (1H, dd, $J=9.5, 1.8$ Hz), 7.65-7.63 (1H, m). LCMS (M+H) calcd for C₉H₆N₄F: 189.05; found: 189.13.

Intermediate 35

*(4-Fluoro-2-(1H-1,2,4-triazol-1-yl)phenyl)methanamine hydrochloride.*

- 5 Nitrile **33** (2.46 g, 13.13 mmol) was dissolved in hot ethanol (150 mL). Aqueous HCl (15 mL, 1N) was added followed by 10% Pd/C (200 mg). The mixture was shaken under H₂ at 55 psi for 4 h., filtered over celite and concentrated. The residue was partitioned between EtOAc and water. The aqueous phase was lyophilized to give intermediate **35** as a white powder (2.96 g, 99%). ¹H NMR (500 MHz, CD₃OD)
- 10 δ : 9.51 (1H, s), 8.63 (1H, s), 7.85 (1H, dd, J = 8.5, 5.8 Hz), 7.68 (1H, dd, J = 8.8, 2.4 Hz), 7.49 (1H, td, J = 8.3, 2.4 Hz), 4.20 (2H, s). LCMS (M+H) calcd for C₉H₁₀N₄F: 193.08; found: 193.16.

Intermediate 36

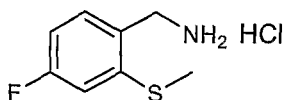


15

(4-Fluoro-2-(1H-1,2,4-triazol-1-yl)phenyl)methanamine hydrochloride.

- Intermediate **36** was prepared (79% yield) following the procedure for intermediate **35** using intermediate **34**. ¹H NMR (500 MHz, CD₃OD) δ : 9.25 (1H, s), 8.46 (1H, s),
- 20 7.80 (1H, dd, J = 8.6, 5.8 Hz), 7.64 (1H, dd, J = 8.8, 2.4 Hz), 7.44 (1H, td, J = 8.3, 2.6 Hz), 4.17 (2H, s). LCMS (M+H) calcd for C₉H₁₀N₄F: 193.08; found: 193.16.

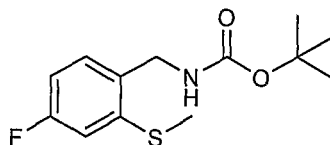
Intermediate 37



5 *4-Fluoro-2-methylsulfanyl-benzylamine*. 4-Fluoro-2-(methylthio)benzonitrile (prepared as in Anthony, N. J. et al. PCT Appl. WO 02/30931, 2002) (1.67 g, 0.1 mol) was dissolved in 20 mL THF and under N₂ treated with 10 mL 2M BH₃.Me₂S. This was heated at 60 °C for 2 hrs. Heating was discontinued and 5mL MeOH was cautiously added, followed by the cautious addition of 4 mL 6N HCl. Then 20 mL more H₂O added and EtOAc and the layers were separated. The aqueous layer was
10 made basic with 1N NaOH and extracted with CH₂Cl₂. The extracts were dried (MgSO₄), filtered, concentrated and dried in vacuum to give intermediate 37 (1.3g, 76%) as a solid. ¹H NMR (500 MHz, CDCl₃) δ: 7.20 - 7.31 (1 H, m) 6.90 (1 H, dd, *J*=2.4 Hz) 6.75 - 6.86 (1 H, m) 3.86 (2 H, s) 2.47 (3 H, s). LC/MS (M+H): 172.

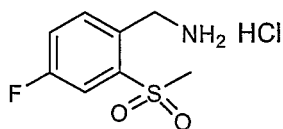
15

Intermediate 38



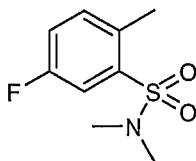
N-t-Butoxycarbonyl-(4-fluoro-2-(methylthio)phenyl)methanamine. A stirred solution of intermediate 37 (5.1g, 0.03 mol) and 3.3g triethylamine in 100mL CH₂Cl₂ under N₂ was treated with di-*t*-butyl dicarbonate (7.2g, 0.033 mol) portionwise and stirred at room temperature for 30 min. Then, the reaction mixture was washed with
20 dil HCl and water. The organic layer was dried over MgSO₄, filtered and concentrated to leave 8.1g (100%) of intermediate 38 as a clear oil. ¹H NMR (500 MHz, CDCl₃) δ: 7.22 - 7.29 (1 H, m) 6.89 (1 H, dd, *J*=9.61, 2.29 Hz) 6.75 - 6.83 (1 H, m) 4.93 (1 H, s) 4.31 (2 H, d, *J*=5.49 Hz) 2.47 (3 H, s) 1.44 (9 H, s). LC/MS
25 (M+H): 272.

Intermediate 39



(4-Fluoro-2-(methylsulfonyl)phenyl)methanamine hydrochloride. A solution of intermediate 38 (8.1g, 0.03 mol) in 100mL acetone and 50mL water was treated with oxone (18.5g, 0.03 mol) and stirred for 10 min. Then an additional 18.5g oxone was added and the mixture was warmed at 60 °C for 1.5 hrs. This was cooled, concentrated to remove acetone and extracted with CH₂Cl₂. This was concentrated to an oil, dissolved in 20 mL ethanol and treated with 10 mL 6N HCl and warmed at 60 °C for 2h. Removal of solvents gave a gum which was crystallized from ethanol to give intermediate 39 (2.0g) as crystals. The aqueous layer was made basic with ammonium hydroxide and extracted further with CH₂Cl₂ and concentration of the extracts gave a gum which was treated with HCl in ethanol to give an additional 0.9g of intermediate 39. ¹H NMR (500 MHz, DMSO-D₆) δ: 8.54 (3 H, s) 7.89 (1 H, dd, J=8.54, 5.19 Hz) 7.67 - 7.85 (2 H, m) 4.40 (2 H, s) 3.41 (3 H, s). LC/MS (M+H) = 204.

Intermediate 40

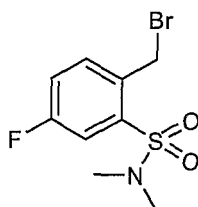


5-Fluoro-2,N,N-trimethyl-benzenesulfonamide. To a solution of 5-fluoro-2-methyl-benzenesulfonyl chloride (4.18 g, 20 mmol) in THF (25 mL) was added dropwise in 15 min a solution of dimethylamine in THF (2M, 25 mL, 50 mmol) under nitrogen and the mixture stirred for 5 min. The insoluble materials formed were filtered and the filtrate concentrated. The residue was purified by column chromatography (SiO₂, 5 % Et₂O in CH₂Cl₂) to obtain intermediate 40 (4.3 g, 90 %) as a clear oil. ¹H NMR (500 MHz, CDCl₃) δ: 2.57 (3 H, s) 2.82 (3 H, s) 2.82 (3 H, s)

7.12 - 7.18 (1 H, m) 7.28 (1 H, dd, $J=8.2, 5.5$ Hz) 7.59 (1 H, dd, $J=8.2, 2.1$ Hz).

LC/MC (M+H): 218.

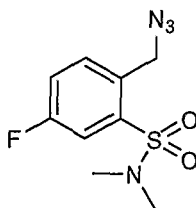
Intermediate 41



5

- 2-Bromomethyl-5-fluoro-N,N-dimethylbenzenesulfonamide. A mixture of intermediate 40 (435 mg, 2.0 mmol) and N-bromosuccinimide (391 mg, 2.2 mmol) in CCl_4 (20 mL) was stirred in an oil bath heated at 80-90 °C under nitrogen for 5 min.
- 10 To this mixture was added 2,2'-azobisisobutyronitrile (AIBN, 100 mg) and the mixture continued to heat at 80-90 °C for 30 min. After cooling, the insoluble precipitates were filtered and the filtrate concentrated and purified by column chromatography (SiO_2 , CH_2Cl_2) to obtain intermediate 41 (440 mg, 74 %). ^1H NMR (500 MHz, CDCl_3) δ : 2.87 (6 H, s) 4.86 (2 H, s) 7.28 (1 H, dd, $J=8.55, 2.75$ Hz) 7.61
- 15 - 7.65 (2 H, m). LC/MC (M+H): 296/298.

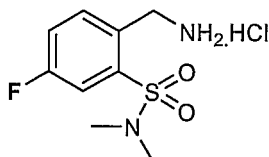
Intermediate 42



- 20 2-Azidomethyl-5-fluoro-N,N-dimethylbenzenesulfonamide. A mixture of intermediate 41 (880 mg, 2.97 mmol) and sodium azide (200 mg, 3 mmol) in DMF (4 mL) was stirred under nitrogen in an oil bath heated at 55-60 °C for 30 min and the solvent was removed in vacuo. The residue was partitioned between CH_2Cl_2 and water, and the organic phase was washed with water, dried (Na_2SO_4), filtered and

concentrated to obtain intermediate **42** (670 mg, 87 %) of as a yellow oil. ^1H NMR (500 MHz, CDCl_3) δ : 2.84 (6 H, s) 4.78 (2 H, s) 7.29 - 7.34 (1 H, m) 7.59 - 7.64 (2 H, m).

5

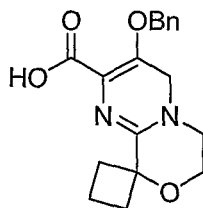
Intermediate **43***2-(aminomethyl)-5-fluoro-N,N-dimethylbenzenesulfonamide hydrochloride.*

To a solution of intermediate **42** (660 mg, 2.6 mmol) in THF (10 mL) and water (2
10 mL) was added triphenylphosphine (740 mg, 2.8 mmol), and the mixture stirred
under nitrogen for 1 h. The THF was evaporated in vacuo and a mixture of the
residue and 6N HCl (3 mL) in MeOH (5 mL) was heated in an oil bath at 80 °C for
20 h. This was washed with CH_2Cl_2 , and the aqueous phase basified with dilute
 NH_4OH and extracted with CH_2Cl_2 . The organic extract was dried (Na_2SO_4), filtered
15 and concentrated to obtain free amine **43** (210 mg, 35 %) as an oil. ^1H NMR (500
MHz, CDCl_3) δ : 2.84 (6 H, s) 4.10 (2 H, s) 7.23 - 7.29 (1 H, m) 7.53 - 7.60 (2 H, m);
LC/MS (M+H): 233.

Alternatively, a solution of intermediate **42** (23.6 g, 91.37 mmol) in EtOH
20 (100 mL) and 5M aq. HCl (22 mL) was degassed by bubbling N_2 through it for 5
min. and 10%Pd/carbon (2.0 g) was added. This mixture was evacuated and vented
to H_2 (repeated three times) and left on Parr shaker for 20 h under H_2 (40 psi)
atmosphere. The reaction mixture was filtered, concentrated and resulting residue
was taken up in water (200 mL). This was extracted with EtOAc (3 X 50 mL). The
25 organic layer discarded and aqueous layer freeze dried to afford **43** (16.3 g, 66%) as
pale yellow powder.

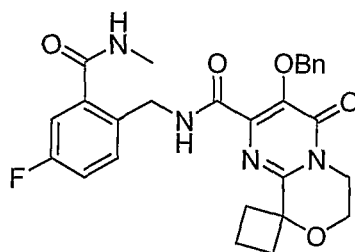
57

Intermediate 44



To a solution of intermediate **28** (0.103 g, 0.367 mmol) in anhydrous dimethylformamide (4 mL) was added anhydrous potassium carbonate (0.206 g, 1.47 mmol) and benzyl bromide (0.071 g, 0.39 mmol), and the reaction was stirred with heating (60 °C) for 18 hours under nitrogen atmosphere. To the reaction mixture was added lithium hydroxide (0.024 g, 0.92 mmol), water (5 mL) and ethanol (5 mL). The reaction was stirred (60 °C) for 2 hours, after which HPLC indicated reaction was complete. The solvent was removed *in vacuo*, and the crude product was dissolved in water (~10 mL) and brought to pH 1-2 using 6 N hydrochloric acid. The product was extracted with ethyl acetate (3 x 30 mL), dried (Na₂SO₄), filtered and concentrated to give 0.13 g (100%) of intermediate **44** as an oil which solidified upon standing. The intermediate was used in the following reaction without further purification: ¹H NMR (500 MHz, CDCl₃) δ: 7.54 (2H, d, *J*=7.3 Hz), 7.30 - 7.38 (3H, m), 5.49 (2H, s), 3.95 - 4.01 (4H, m), 2.67 - 2.74 (2H, m), 2.33 - 2.41 (2H, m), 2.06 - 2.14 (2H, m).

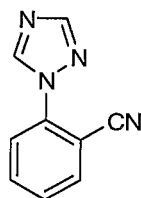
Intermediate 45



20

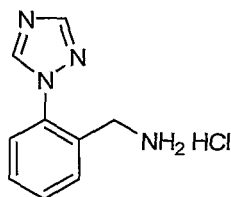
To a solution of intermediate **44** (obtained above) in dimethylformamide (3 mL) was added *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU, 0.167 g, 0.44 mmol) and the mixture was stirred for 20

minutes. To this was added 2-(aminomethyl)-5-fluoro-N-methylbenzamide hydrochloride (prepared according to M. Egbertson et al PCT Appl. WO 03077850) and *N,N*-dimethylaminopyridine (0.068 g, 0.55 mmol) and the reaction was stirred for 16 hours. The solvent was removed *in vacuo* and the crude product in ethyl acetate (25 mL) was washed with 1.0 N hydrochloric acid (25 mL), then dried (Na₂SO₄), filtered, and concentrated to give an orange-brown solid. This was purified by flash silica gel column chromatography, eluting with 30% to 60% ethyl acetate in hexanes, to give a colorless oil. The oil was triturated with diethyl ether and dried *in-vacuo* to give intermediate **45** (0.101 g, 54% over two steps) as a white glassy solid: ¹H NMR (500 MHz, CDCl₃) δ: 8.62 (1H, t, *J*=6.1 Hz), 7.44-7.51 (3H, m), 7.27-7.33 (3H, m), 7.13 (1H, dd, *J*=8.9, 2.7 Hz), 7.08 (1H, dt, *J*=8.2, 2.7 Hz), 6.49-6.58 (1H, m), 5.28 (2H, s), 4.56 (2H, d, *J*=6.4 Hz), 3.90-4.00 (4H, m), 2.98 (3H, d, *J*=4.9 Hz), 2.71-2.79 (2H, m), 2.26-2.36 (2H, m), 2.14-2.24 (1H, m), 2.04-2.11 (1H, m). LC/MS (*M*+*H*) 507.13.

Intermediate **46**

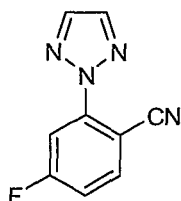
2-(1H-1,2,4-triazol-1-yl)benzonitrile: A suspension of 2-fluorobenzonitrile (3.0 g, 25 mmol) and 1,2,4-triazole sodium complex (2.4 g, 27 mmol) were stirred in THF (7 mL) and DMF (14 mL) at 95° C for 18 h. After cooling and concentrating, the product was crystallized from hot CH₂Cl₂/hexane (1:1) to give the title compound as a white solid (4.25 g, 100% yield). ¹H-NMR (300 MHz, CDCl₃) δ: 8.74 (1H, s), 8.16 (1H, s), 7.82 (1H, dd, *J*= 4.9, 1.3 Hz), 7.77-7.25 (2H, m), 7.57-7.51 (1H, m). LCMS [*M*+*H*]⁺ calcd for C₉H₇N₄: 171.06; found: 171.12.

Intermediate 47



5 2-(1H-1,2,4-triazol-1-yl)phenylmethanamine hydrochloride: Intermediate 46
(4.25 g, 25 mmol) was dissolved in EtOH (50 mL) and 1N HCl (25 mL). Added
Pd/C (1 g) and mixture was shaken under H₂ for 2 h at 50 psi. After filtration over
celite and concentration, the residue was triturated with diethyl ether and the title
compound was collected as a white solid (3.94 g, 75% yield). ¹H-NMR (300 MHz,
10 CD₃OD) δ: 9.01 (1H, s), 8.32 (1H, s), 7.78-7.64 (4H, m), 4.15 (2H, s). LCMS
[M+H]⁺ calcd for C₉H₁₁N₄: 175.09; found: 175.17.

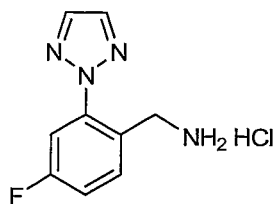
Intermediate 48



15
20 4-Fluoro-2(2H-1,2,3-triazol-2-yl)benzonitrile: To a solution of 1H-1,2,3-
triazole (3.5 g, 50.7 mmol) in THF (10 mL) and DMF (20 mL) was added
portionwise, NaH (1.3 g, 51 mmol, 95%). The mixture was stirred at room temp for
30 min. Added to this was 2,4-difluorobenzonitrile (7.6 g, 55 mmol) and the mixture
was stirred at 85° C for 3 h. The white mixture was concentrated and purified by
flash chromatography eluting with 0%-5%-10% EtOAc/hexane to give the title
compound as white needles (0.34 g, 3% yield). ¹H-NMR (300 MHz, CDCl₃) δ: 7.92
(2H, s), 7.88-7.79 (2H, m), 7.19-7.12 (1H, m). LCMS [M+H]⁺ calcd for C₉H₆N₄F:
25 189.05; found: 189.12.

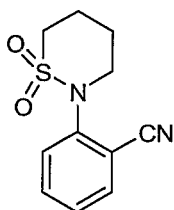
60

Intermediate 49

5 *4-Fluoro-2-(2H-1,2,3-triazol-2-yl)phenylmethanamine hydrochloride:*

Intermediate 48 (0.34 g, 1.8 mmol) was dissolved in EtOH (50 mL). Added to this solution was 1N HCl (10 mL) and catalytic Pd/C. The mixture was shaken under H₂ at 55 psi for 4 h, filtered over celite and concentrated to give the title compound as a yellow solid (0.4021 g, 98 % yield). ¹H-NMR (500 MHz, CD₃OD) δ: 8.13 (2H, s),
 10 7.87 (1H, dd, *J* = 4.9, 2.6 Hz), 7.73 (1H, dd, *J* = 4.9, 2.6 Hz), 7.34 (1H, td, *J* = 8.2, 2.7 Hz), 4.35 (2H, s). LCMS [*M*+H]⁺ calcd for C₉H₁₀N₄F: 193.08; found: 193.16.

Intermediate 50



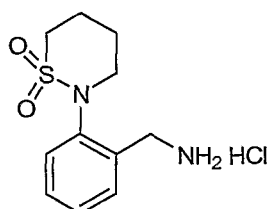
15

2-(1,1-dioxo-1λ6-[1,2]thiazinan-2-yl)benonitrile: Added to a solution of 1,1-dioxo[1,2]thiazinane (3.37 g, 25 mmol) in DMF (35 mL) was sodium hydride (0.675 g, 25 mmol, 95%) and the mixture was stirred at room temp for 15 min. 2-
 20 Fluorobenzonitrile (3.37 mL, 31.3 mmol) was added and the mixture was stirred at 80° C for 18 h. The mixture was cooled, diluted with water and extracted with EtOAc. The organic phase was washed with water and brine, dried (Na₂SO₄) and concentrated. The residue was purified by flash chromatography eluting with 10%-100% EtOAc/hexane. The isolated solid was recrystallized from hot EtOAc/hexane
 25 (2:1) to give the title compound as white crystals (4.15 g, 70% yield). ¹H-NMR (300 MHz, CDCl₃) δ: 7.70 (1H, dd, *J* = 7.7, 1.1 Hz), 7.64-7.53 (2H, m), 7.41 (1H, td, *J* =

7.3, 1.6 Hz), 3.72 (2H, t, $J = 5.5$ Hz), 3.32 (2H, t, $J = 6.0$ Hz), 2.40-2.32 (2H, m), 2.05-1.97 (2H, m). LCMS $[M+H]^+$ calcd for $C_{11}H_{12}N_2O_2S$: 237.06; found: 237.10.

Intermediate 51

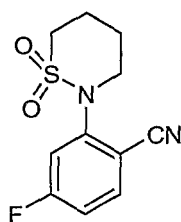
5

*2-(1,1-dioxo-1λ6-[1,2]thiazinan-2-yl)benzylamine hydrochloride:*

Intermediate 50 (2.63 g, 11.14 mmol) was dissolved in EtOH (150 mL) and 1N HCl (13 mL). Added to this was Pd/C (0.5 g) and the mixture was shaken under H_2 at 55 psi for 24 h. Filtration over celite and concentration gave the title compound as a white solid (2.93 g, 95% yield). 1H -NMR (300 MHz, CD_3OD) δ : 7.61-7.47 (4H, m), 4.30 (2H, q, $J = 13.7$ Hz), 3.96-3.87 (1H, m), 3.49-3.36 (3H, m), 2.40-2.31 (2H, m), 2.05-1.96 (2H, m). LCMS $[M+H]^+$ calcd for $C_{11}H_{17}N_2SO_2$: 241.10; found: 241.10.

15

Intermediate 52



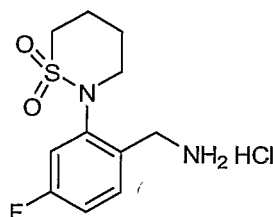
20 *4-Fluoro-2-(1,1-dioxo-1λ6-[1,2]thiazinan-2-yl)benzonitrile:* To a solution of 1,1-dioxo[1,2]thiazinane (8.84 g, 65.4 mmol) in DMF (20 mL) and THF (10 mL) was added portion-wise sodium hydride (1.65 g, 65.5 mmol, 95%). After stirring for 30 min, 2,4-difluorobenzonitrile (10.0 g, 72 mmol) was added and the mixture was stirred at 90° C for 2.5 h. The mixture was cooled and concentrated and the residue was purified by flash chromatography eluting with 0%-10% EtOAc/hexane to give the title compound as white needles (1.37 g, 8% yield). 1H -NMR (500 MHz, $CDCl_3$)

25

δ : 7.70 (1H, dd, $J = 8.8, 5.8$ Hz), 7.30 (1H, dd, $J = 8.8, 2.4$ Hz), 7.15-7.12 (1H, m), 3.72 (2H, t, $J = 5.3$ Hz), 3.33 (2H, t, $J = 6.1$ Hz), 2.40-2.35 (2H, m), 2.05-2.01 (2H, m). LCMS $[M+H]^+$ calcd for $C_{11}H_{12}N_2FO_2S$: 255.06; found: 255.19.

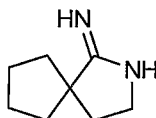
5

Intermediate 53

*4-Fluoro- 2-(1,1-dioxo-1,2,3,4-tetrahydrothiazin-2-yl)benzylamine hydrochloride:*

- 10 Following the procedure for Intermediate 51 using Intermediate 52 (1.37 g, 5.4 mmol) gave the title compound as a white solid (1.58 g, 100 % yield). 1H -NMR (300 MHz, CD_3OD) δ : 7.61 (1H, dd, $J = 8.4, 6.2$ Hz), 7.38 (1H, dd, $J = 9.3, 2.7$ Hz), 7.28 (1H, td, $J = 8.2, 2.7$ Hz), 7.26 (2H, dd, $J = 21.4, 13.7$ Hz), 3.93-3.84 (1H, m), 3.50-3.41 (3H, m), 2.40-2.31 (2H, m), 2.04-1.96 (2H, m). LCMS $[M+H]^+$ calcd for
- 15 $C_{11}H_{16}N_2FO_2S$: 259.09; found: 259.24.

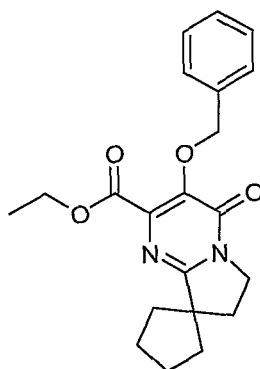
Intermediate 54



20

- To a solution of 1-(2-chloroethyl)cyclopentanecarbonitrile (1.38g, 8.73 mmol; prepared according to R. M. Burk et al Heterocycles **1993**, 35, 205) in 40 mL MeOH was added 1 mmol sodium iodide and the solution was saturated with ammonia. The reaction bottle was sealed and warmed at 90°C with stirring for 20 h. After cooling
- 25 the reaction bottle was opened and solvents were evaporated under vacuum. LC/MS (M+H): 139. 1H NMR (500 MHz, $CDCl_3$) δ : 1.50-2.33 (10H, m), 3.53-3.78 (2H, m).

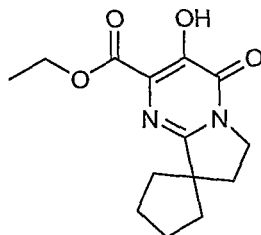
Intermediate 55



5 To a solution of diethyl-2-(benzyloxy)-3-hydroxyfumarate [prepared from benzyloxy ethylacetate (2.91g, 0.015 mol) and diethyl oxalate (2.19g, .015 mol) with an equivalent amount of sodium hydride in 40 mL THF and 2 drops EtOH by stirring for 30 min] in 20 mL EtOH was added intermediate **54** in 10 mL EtOH and with stirring 60% NaH (300mg, 0.0075 mol) was added portionwise. This was stirred for 10 3 h at rt and concentrated. The residue was dissolved in CH₂Cl₂ and washed with water. The CH₂Cl₂ layer was dried over MgSO₄, filtered and concentrated. Chromatography on silica and elution with 9:1 CH₂Cl₂:Et₂O gave 600mg of the title compound **55** (Yield = 19%). LC/MS (M+H): 369. ¹H NMR (500 MHz, CDCl₃) δ : 1.29 (3H, t, *J* = 7.2 Hz), 1.56 (1H, s), 1.68-1.80 (3H, m), 1.85-1.96 (1H, m), 2.04- 15 2.17 (3H, m), 4.03-4.08 (1H, m), 4.03-4.10 (2H, m), 4.22 (1H, q, *J* = 7.0 Hz), 4.32 (1H, q, *J* = 7.0 Hz), 4.63 (1H, s), 5.24 (2H, s), 7.28-7.40 (3H, m), 7.47 (2H, d, *J* = 6.7 Hz).

Intermediate 56

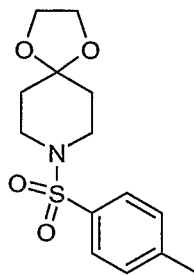
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Intermediate **55** was dissolved in 15 mL TFA and stirred at rt for 16h. The TFA was removed and the crude chromatographed on C18 using 10% CH₃CN/ H₂O initially as eluant. Product eluted with 20% CH₃CN. Pure fractions were concentrated and extracted with CH₂Cl₂. Evaporation of the solvent left 300 mg (Yield = 51%) of the title compound **56**. LC/MS (M+H): 279. ¹H NMR (300 MHz, CDCl₃) δ: 1.41 (3H, t, *J* = 7.1 Hz), 1.65-1.79 (4H, m), 1.84-1.97 (2H, m), 2.00-2.12 (4H, m), 3.98-4.08 (2H, m), 4.44 (2H, q, *J* = 7.0 Hz), 10.78 (1H, s).

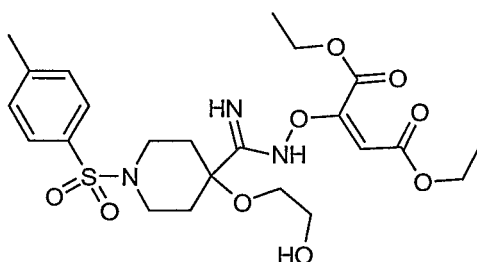
Intermediate **57**

10



To a solution of 1,4-dioxaspiro[4,5]decane (10.0 g, 70 mmol) and triethylamine (20 mL, 142 mmol) in diethylether (50 mL) cooled to 0° C was added dropwise tosyl chloride (13.5 g, 71 mmol) dissolved in CH₂Cl₂. The resulting suspension was stirred at room temperature 5 h. and washed with saturated aqueous NaHCO₃, water and dried (Na₂SO₄). Concentration gave the Intermediate **57** as a white solid (20.20 g, 97%). ¹H-NMR (300 MHz, CDCl₃) δ: 7.61 (2H, d, *J* = 8.0 Hz), 7.28 (2H, d, *J* = 8.0 Hz), 3.86 (4H, s), 3.11 (4H, t, *J* = 5.8 Hz), 2.40 (3H, s), 1.75 (4H, t, *J* = 5.8 Hz). LCMS (M+H) calcd for C₁₄H₂₀NO₄S: 298.11; found: 298.16.

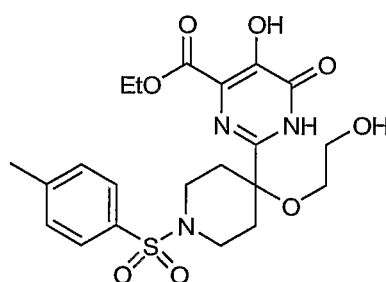
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Intermediate **58**

To a stirred solution of zinc iodide (2.05 g, 6.26 mmol) and Intermediate **57** (9.3 g, 31.3 mmol) in dichloromethane (10 mL) was added trimethylsilylcyanide (4.29 mL, 31.3 mmol) with water bath cooling. The resulting mixture was stirred at room temp for 2 h and concentrated. The amber oil was used in the next step without purification.

To solution of above crude in EtOH (60 mL) was added hydroxylamine (2.1 mL, 31.3 mmol, 50wt% in water) and the resulting mixture was stirred at room temperature. After 18 h diethylacetylenedicarboxylate (6.0 mL, 37.5 mmol) was added and stirred for additional 3 days and concentrated. The residue was purified by flash chromatography eluting with 0%-25%-50% EtOAc/Hexane to give the Intermediate **58** as a yellow foam (11.72 g, 71%). ¹H-NMR (300 MHz, CDCl₃) δ: 7.62 (2H, t, *J* = 7.7 Hz), 7.30 (2H, t, *J* = 8.2, 2.0 Hz), 5.27 (1H, s), 4.34-4.23 (2H, m), 4.19-4.05 (2H, m), 3.68-3.66 (2H, m), 3.54-3.49 (2H, m), 3.34-3.28 (2H, m), 2.72 (1H, dt, *J* = 11.4, 2.5 Hz), 2.66-2.57 (1H, m), 2.40 (3H, d, *J* = 1.6 Hz), 2.05-1.89 (4H, m), 1.35-1.22 (6H, m). LCMS (M+H) calcd for C₂₃H₃₄N₃O₉S: 528.20; found: 528.13.

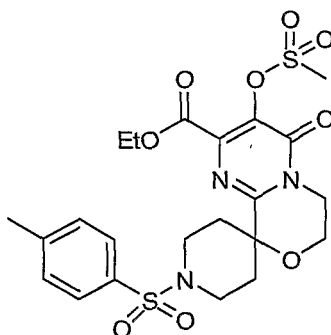
Intermediate **59**



1,2,4-trimethylbenzene (100 mL) was added to Intermediate **58** (11.7 g, 22 mmol) and the mixture was stirred at 140° C for 3 h. The mixture was cooled to room temp and concentrated. Residue dissolved in CH₂Cl₂ and insoluble solids removed by filtration and discarded. Concentration gave the Intermediate **59** as a brown foam (5.02 g, 47% yield). LCMS (M+H) calcd for C₂₁H₂₈N₃O₈S: 482.16; found: 482.11.

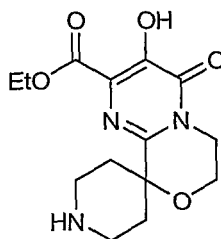
66

Intermediate 60



- 5 A solution of Intermediate 59 (3.0 g, 6.2 mmol) and triethylamine (2.5 mL, 18.7 mmol) in CH_2Cl_2 (8 mL) was cooled to 0°C . To this was added to methanesulfonylchloride (0.47 mL, 6.3 mmol) and the resulting mixture was stirred while gradually warming to room temperature for 18 h. The mixture was washed with water and the organic phase was dried (Na_2SO_4) to give a brown foam that was
- 10 purified by flash chromatography eluting with 10%-50% EtOAc/hexane to give the Intermediate 60 as a yellow foam (0.477 g, 14% yield). ^1H -NMR (300 MHz, CDCl_3) δ : 7.63 (2H, d, $J = 8.4$ Hz), 7.31 (2H, d, $J = 8.0$ Hz), 4.41 (2H, q, $J = 7.3$ Hz), 3.92-3.89 (2H, m), 3.73-3.68 (1H, m), 3.49 (3H, s), 3.49-3.42 (1H, m), 2.63-2.48 (2H, m), 2.43-2.41 (4H, m), 1.94-1.90 (2H, d, $J = 13.5$ Hz), 1.39 (3H, t, $J = 7.1$ Hz). LCMS
- 15 (M+H) calcd for $\text{C}_{22}\text{H}_{28}\text{N}_3\text{O}_9\text{S}_2$: 542.12; found: 542.03.

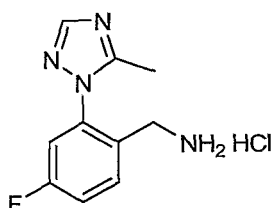
Intermediate 61



20

To a stirred solution of Intermediate 60 (0.411 g, 0.76 mmol) in THF (10 mL) at cooled to -78°C was added dropwise a freshly prepared mixture of sodium (0.42 g, 20 mmol) dissolved in Naphthalene (2.56 g, 20 mmol) and THF (20 mL) until the

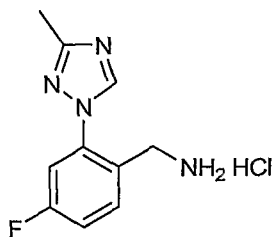
blue color persisted. The resulting mixture stirred an additional 1 h and was quenched with 1N HCl. The aqueous layer was washed with EtOAc and freeze dried. The solids were purified by preparative HPLC (YMC Combiprep ODS-A, 30mm x 50mm, MeOH/H₂O/0.1% TFA), to give the Intermediate **61** as a white solid (0.024 g, 10% yield). LCMS (M+H) calcd for C₁₄H₂₀N₃O₅: 310.14; found: 310.10.

Intermediate **62**

10

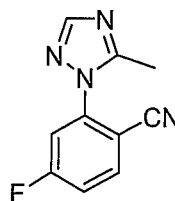
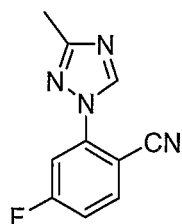
(4-fluoro-2-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)methanamine hydrochloride: Intermediate **62** was prepared according to procedure for intermediate **35**. LCMS (M+H): 207.2.

15

Intermediate **63**

(4-fluoro-2-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)methanamine hydrochloride: Intermediate **63** was prepared according to procedure for intermediate **35**. LCMS (M+H): 207.2.

25

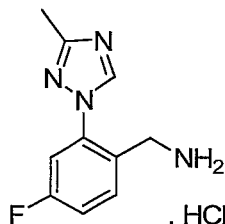
Intermediate **64** and **65**

5 *4-Fluoro-2-(3-methyl-1H-1,2,4-triazol-1-yl)benzonitrile* and *4-fluoro-2-(5-methyl-1H-1,2,4-triazol-1-yl)benzonitrile*. A solution of 2,4-difluorobenzonitrile (7.07 g, 50.8 mmol) and 3-methyl-1H-1,2,4-triazole (4.22 g, 50.8 mmol) in N,N-dimethylformamide (45 ml) was treated with powdered anhydrous potassium carbonate (10 g) and the resulting mixture was stirred at 22 °C for 18h. The solid
10 was then filtered and the filtrate was concentrated *in vacuo*. The residue was diluted with ethyl acetate, washed with water and brine, dried over anhydrous magnesium sulfate and concentrated. The mixture containing the 2 and 4-triazolyl-benzonitriles was purified by a combination of chromatography on silica gel (elution gradient of ethyl acetate in hexane) and on reversed phase silica gel to give 1.86 g (18 % yield)
15 of Intermediate **64** and 0.526 g (5 % yield) of Intermediate **65**.

4-Fluoro-2-(3-methyl-1H-1,2,4-triazol-1-yl)benzonitrile. white crystals (ethyl acetate – hexane) ; mp 117 - 118 °C. ¹HNMR 400 MHz (CDCl₃) δ (ppm) : 2.54 (3H, s, CH₃), 7.24 (1H, m, CH), 7.62 (1H, dd, J = 2.5 Hz and J = 9.1 Hz, CH), 7.84 (1H, dd, J = 5.6 Hz and J = 8.6 Hz, CH), 8.82 (1H, s, CH). Anal. Calcd for C₁₀H₇FN₄: C 59.40, H 3.49, N 27.71; Found: C 59.25, H 3.32, N 27.81.
20

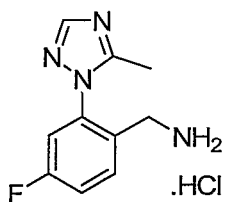
4-fluoro-2-(5-methyl-1H-1,2,4-triazol-1-yl)benzonitrile. white crystals (ethyl acetate – hexane); mp 120 - 121 °C. ¹HNMR 400 MHz (CDCl₃) δ (ppm) : 2.56 (3H, s, CH₃), 7.30 (1H, dd, J = 2.5 Hz and J = 8.1 Hz, CH), 7.39 (1H, m, CH), 7.91 (1H, dd, J = 5.5 Hz and J = 8.6 Hz, CH), 8.06 (1H, s, CH). Anal. Calcd for C₁₀H₇FN₄: C 59.40, H 3.49, N 27.71; Found: C 59.35, H 3.70, N 27.77.
25

Intermediate 66



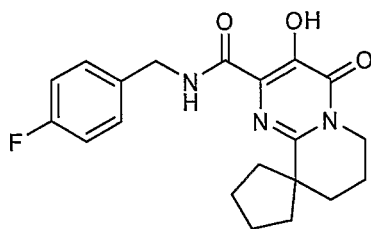
- 5 *(4-Fluoro-2-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)methanamine hydrochloride salt.* Hydrogenation of 4-fluoro-2-(3-methyl-1H-1,2,4-triazol-1-yl)benzonitrile (0.680 g, 3.36 mmol) gave 0.720 g (88 % yield) of the title hydrochloride salt as a white solid. ¹HNMR 400 MHz (DMSO-d₆) δ (ppm) : 2.40 (3H, s, CH₃), 4.02 (2H, m, NCH₂), 7.50 (1H, m, CH), 7.62 (1H, dd, J = 2.8 Hz and J = 9.3 Hz, CH), 7.84 (1H, dd, J = 6.1 Hz and J = 9.1 Hz, CH), 9.00 (1H, s, CH).
 10 HRMS (ESI⁺) calculated for C₁₀H₁₂FN₄ [M+H⁺] : 207.1046 ; found : 207.1047.

Intermediate 67



- 15 *(4-Fluoro-2-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)methanamine hydrochloride salt.* Hydrogenation of 4-fluoro-2-(5-methyl-1H-1,2,4-triazol-1-yl)benzonitrile (0.244 g, 1.20 mmol) gave 0.290 g (100 % yield) of the title hydrochloride salt as a white solid. ¹HNMR 400 MHz (DMSO-d₆) δ (ppm) : 2.42 (3H, s, CH₃), 3.78 (2H, m, NCH₂), 7.58 (1H, m, CH), 7.67 (1H, dd, J = 2.8 Hz and J = 9.3 Hz, CH), 7.90 (1H, dd, J = 6.0 Hz and J = 8.6 Hz, CH), 8.22 (1H, s, CH).
 20 HRMS (ESI⁺) calculated for C₁₀H₁₂FN₄ [M+H⁺] : 207.1046 ; found : 207.1041.

Example 1

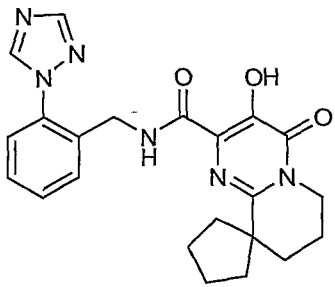
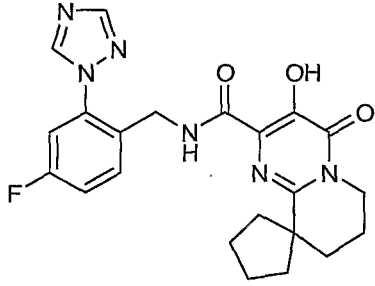
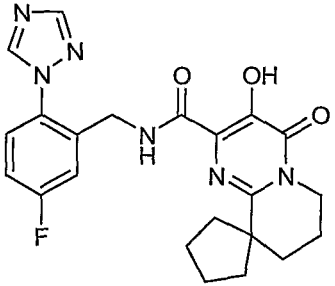


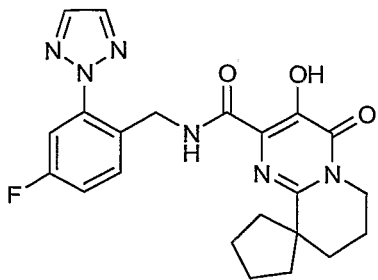
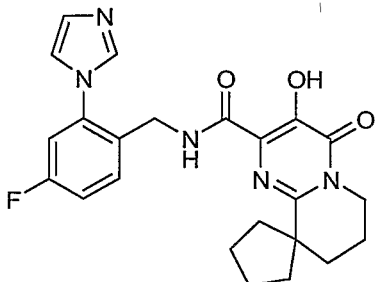
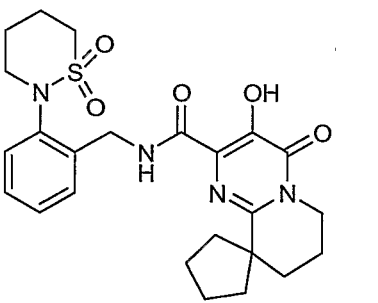
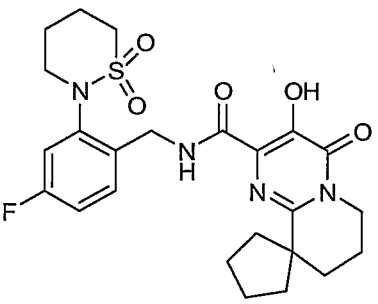
A mixture of ester **3** (0.146 g, .499 mmol), 4-fluorobenzylamine (0.156 g, 1.25 mmol, and triethylamine (0.14 mL, 1 mmol) in 1:1 DMF/EtOH (2 mL) was heated at 110 °C for 1.5 h. Then, the reaction mixture was cooled and purified preparative HPLC using MeOH/water containing 0.1% TFA (gradient elution). The fractions containing the product were combined and evaporated to afford the product as a white solid (0.0955g, 51.5%). ¹H NMR (500 MHz, CDCl₃) δ: 11.70 (1H, s), 7.86 (1H, br t), 7.32-7.29 (2H, m), 7.05 (2H, t, J = 8.6 Hz), 4.59 (2H, d, J = 6.4 Hz), 4.01 (2H, t, J = 6.4 Hz), 2.16-2.11 (2H, m), 1.99-1.94 (2H, m), 1.82-1.65 (8H, m). HRMS (M+H) calcd for C₂₀H₂₃FN₃O₃: 372.1724; found: 371.1714. Anal calcd for C₂₀H₂₂FN₃O₃: C, 64.67; H, 5.97; N, 11.31. Found: C, 64.58; H, 6.24; N, 11.11.

Other examples made by similar methods using amine (2-10 equiv), Et₃N (2-10 equiv.) and appropriate ester in DMF, DMF/EtOH, or other solvent system at 60 °C-140 °C are listed in Table 3.

Table 3.

Ex.	Structure	Data
2		Yield: 43%. ¹ H NMR (500 MHz, CDCl ₃) δ: 11.72 (1H, s), 7.84 (1H, br t), 7.15-7.09 (2H, m), 6.99 (1H, t, J = 8.9 Hz), 4.55 (2H, d, J = 6.1 Hz), 4.01 (2H, t, J = 6.4 Hz), 2.28 (3H, s), 2.17-2.12 (2H, m), 1.99-1.94 (2H, m), 1.83-1.65 (8H, m). HRMS (M+H) calcd for C ₂₁ H ₂₅ FN ₃ O ₃ : 386.188; found: 386.1875. Anal calcd for C ₂₁ H ₂₄ FN ₃ O ₃ •0.03 H ₂ O•0.05 CH ₂ Cl ₂ : C, 64.79; H, 6.24; N, 10.77; found: C, 64.71; H, 6.31; N, 10.71.

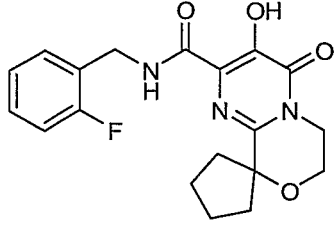
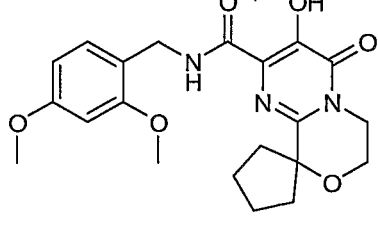
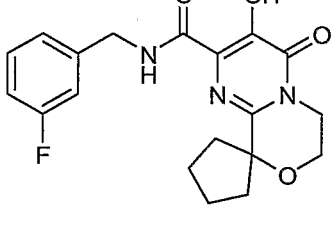
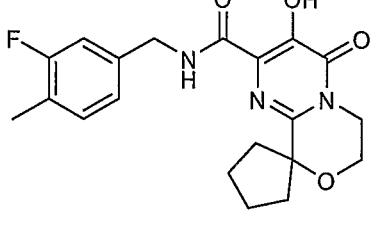
Ex.	Structure	Data
3		Yield: 65%. ¹ H NMR (500 MHz, CDCl ₃) δ: 11.82 (1H, s), 8.80 (1H, t, J = 6.1 Hz), 8.43 (1H, s), 8.15 (1H, s), 7.73 (1H, dd, J = 7.3, 1.5 Hz), 7.52-7.44 (2H, m), 7.36 (1H, dd, J = 7.6, 1.2 Hz), 4.48 (2H, d, J = 6.7 Hz), 3.99 (2H, t, J = 6.4 Hz), 2.28-2.23 (2H, m), 1.99-1.91 (4H, m), 1.79-1.66 (6H, m). HRMS (M+H) calcd for C ₂₂ H ₂₅ N ₆ O ₃ : 421.1988; found: 421.2001. Anal calcd for C ₂₂ H ₂₄ N ₆ O ₃ : C, 62.84; H, 5.75; N, 19.98; found: C, 62.55; H, 5.68; N, 20.03.
4		Yield: 70%. ¹ H NMR (500 MHz, CDCl ₃) δ: 11.76 (0.6H, s), 11.69 (0.4H, s), 8.77 (0.6H, t, J = 6.4 Hz), 8.68 (0.4H, t, J = 6.4 Hz), 8.44 (0.6H, s), 8.39 (0.4H, s), 8.16 (0.6H, s), 8.15 (0.4H, s), 7.73 (0.4H, dd, J = 8.6, 6.1 Hz), 7.43 (0.4H, dd, J = 8.6, 2.8 Hz), 7.34 (0.4H, dd, J = 8.5, 4.9 Hz), 7.21 (0.6H, td, J = 8.2, 2.4 Hz), 7.15 (0.4H, td, J = 8.5, 3.0 Hz), 7.11 (0.6H, dd, J = 8.6, 2.4 Hz), 4.45 (0.6H, d, J = 6.7 Hz), 4.43 (0.4H, d, J = 7.0 Hz), 4.04-3.98 (2H, m), 2.27-2.22 (2H, m), 1.98-1.91 (4H, m), 1.81-1.66 (6H, m). HRMS (M+H) calcd for C ₂₂ H ₂₄ FN ₆ O ₃ : 439.1894; found: 439.1887. Anal calcd for C ₂₂ H ₂₃ FN ₆ O ₃ : C, 60.26; H, 5.28; N, 19.16; found: C, 60.10; H, 5.42; N, 19.25.
5		Yield: 71%. ¹ H NMR (500 MHz, CDCl ₃) δ: 11.77 (0.6H, s), 11.70 (0.4H, s), 8.80 (0.6H, t, J = 6.7 Hz), 8.70 (0.4H, t, J = 6.4 Hz), 8.44 (0.6H, s), 8.39 (0.4H, s), 8.16 (0.6H, s), 8.15 (0.4H, s), 7.73 (0.6H, dd, J = 8.5, 6.1 Hz), 7.43 (0.4H, dd, J = 8.6, 2.8 Hz), 7.34 (0.4H, dd, J = 8.9, 4.9 Hz), 7.21 (0.6H, td, J = 8.2, 2.7 Hz), 7.15 (0.4H, td, J = 8.6, 2.8 Hz), 7.11 (0.6H, dd, J = 8.4, 2.6 Hz), 4.45 (0.6H, d, J = 6.7 Hz), 4.43 (0.4H, d, J = 6.7 Hz), 4.01-3.98 (2H, m), 2.27-2.22 (2H, m), 1.98-1.92 (4H, m), 1.80-1.66 (6H, m). HRMS (M+H) calcd for C ₂₂ H ₂₄ FN ₆ O ₃ : 439.1894; found: 439.1875. Anal calcd for C ₂₂ H ₂₃ FN ₆ O ₃ : C, 60.26; H, 5.28; N, 19.16; found: C, 60.14; H, 5.38; N, 19.25.

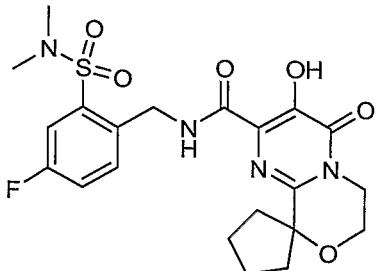
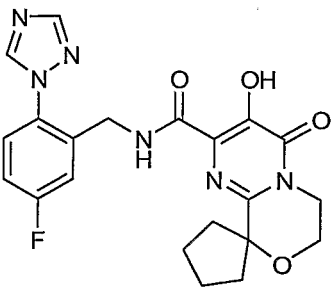
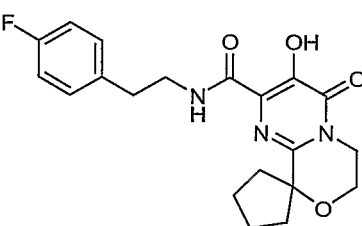
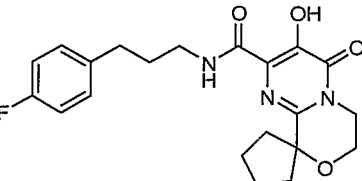
Ex.	Structure	Data
6		Yield: 73%. ^1H NMR (500 MHz, CDCl_3) δ : 11.87 (1H, s), 8.91 (1H, t, $J = 6.7$ Hz), 7.91 (2H, s), 7.69 (1H, dd, $J = 8.5, 5.8$ Hz), 7.63 (1H, dd, $J = 9.3, 2.6$ Hz), 7.13 (1H, td, $J = 8.2, 2.6$ Hz), 4.64 (2H, d, $J = 7.0$ Hz), 3.99 (2H, t, $J = 6.4$ Hz), 2.23-2.17 (2H, m), 1.97-1.85 (4H, m), 1.78-1.63 (6H, m). HRMS (M+H) calcd for $\text{C}_{22}\text{H}_{24}\text{FN}_6\text{O}_3$: 439.1894; found: 439.1912. Anal calcd for $\text{C}_{22}\text{H}_{23}\text{FN}_6\text{O}_3$: C, 60.26; H, 5.28; N, 19.16; found: C, 59.97; H, 4.99; N, 19.03.
7		Yield: 63%. ^1H NMR (500 MHz, CDCl_3) δ : 13.02 (1H, br s), 8.82 (1H, s), 7.98 (1H, t, $J = 5.2$ Hz), 7.60-7.57 (2H, m), 7.47 (1H, s), 7.33 (1H, td, $J = 7.6, 1.8$ Hz), 7.13 (1H, d, $J = 7.3$ Hz), 4.39 (2H, d, $J = 5.8$ Hz), 3.99 (2H, t, $J = 6.4$ Hz), 2.16-2.10 (2H, m), 1.99-1.94 (2H, m), 1.86-1.67 (8H, m). HRMS (M+H) calcd for $\text{C}_{23}\text{H}_{25}\text{FN}_5\text{O}_3$: 438.1941; found: 438.1954. Anal calcd for $\text{C}_{23}\text{H}_{24}\text{FN}_5\text{O}_3 \cdot 0.3 \text{ EtOAc}$: C, 50.92; H, 4.37; N, 10.84; found: C, 50.59; H, 4.14; N, 10.95.
8		Yield: 77%. ^1H NMR (500 MHz, CDCl_3) δ : 11.90 (1H, s), 8.22-8.20 (1H, m), 7.47-7.43 (2H, m), 7.36-7.32 (2H, m), 4.98 (1H, dd, $J = 14.3, 8.5$ Hz), 4.46 (1H, dd, $J = 14.3, 4.0$ Hz), 3.99 (2H, td, $J = 6.2, 1.8$ Hz), 3.90-3.85 (1H, m), 3.44-3.39 (1H, m), 3.25-3.22 (2H, m), 2.44-2.30 (2H, m), 2.23-2.15 (2H, m), 1.97-1.89 (4H, m), 1.85-1.80 (2H, m), 1.73-1.58 (6H, m). HRMS (M+H) calcd for $\text{C}_{24}\text{H}_{31}\text{N}_4\text{O}_5\text{S}$: 487.2015; found: 487.2030. Anal calcd for $\text{C}_{24}\text{H}_{30}\text{N}_4\text{O}_5\text{S}$: C, 59.24; H, 6.21; N, 11.51; found: C, 58.94; H, 6.47; N, 11.43.
9		Yield: 70%. ^1H NMR (500 MHz, CDCl_3) δ : 11.85 (1H, s), 8.22-8.19 (1H, m), 7.46 (1H, dd, $J = 8.6, 6.4$ Hz), 7.16 (1H, dd, $J = 9.2, 2.5$ Hz), 7.06 (1H, td, $J = 8.2, 2.8$ Hz), 4.95 (1H, dd, $J = 14.3, 8.9$ Hz), 4.39 (1H, dd, $J = 14.3, 4.0$ Hz), 3.99 (2H, td, $J = 6.4, 1.8$ Hz), 3.86-3.81 (1H, m), 3.43-3.39 (1H, m), 3.25-3.23 (2H, m), 2.44-2.30 (2H, m), 2.22-2.14 (2H, m), 1.98-1.90 (4H, m), 1.85-1.80 (2H, m), 1.74-1.58 (6H, m). HRMS (M+H) calcd for $\text{C}_{24}\text{H}_{30}\text{FN}_4\text{O}_5\text{S}$: 505.1921; found: 505.1942. Anal calcd for $\text{C}_{24}\text{H}_{29}\text{FN}_4\text{O}_5\text{S}$: C, 57.13; H, 5.79; N, 11.10; found: C, 57.01; H, 5.98; N, 11.02.

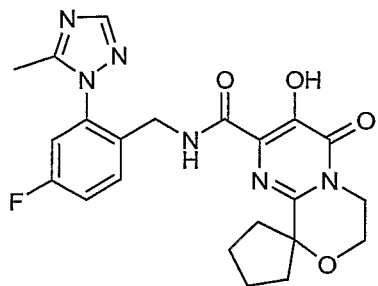
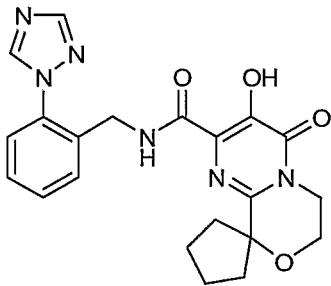
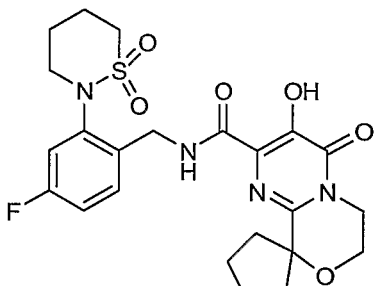
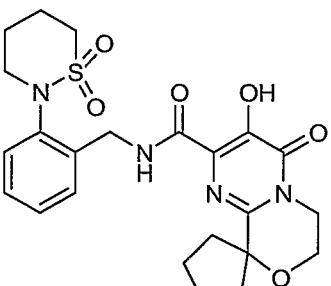
Ex.	Structure	Data
10		Yield: 66%. ^1H NMR (500 MHz, CDCl_3) δ : 11.65 (1H, br s), 8.60 (1H, t, $J = 6.7$ Hz), 7.69 (1H, dd, $J = 8.4, 5.4$ Hz), 7.49 (1H, dd, $J = 8.4, 2.6$ Hz), 7.28-7.24 (1H, m), 4.81 (2H, d, $J = 6.7$ Hz), 3.98 (2H, t, $J = 6.4$ Hz), 2.89 (6H, s), 2.22-2.16 (2H, m), 1.96-1.91 (4H, m), 1.76-1.61 (6H, m). HRMS ($\text{M}+\text{H}$) calcd for $\text{C}_{22}\text{H}_{28}\text{FN}_4\text{O}_5\text{S}$: 479.1764; found: 479.1788. Anal calcd for $\text{C}_{22}\text{H}_{27}\text{FN}_4\text{O}_5\text{S} \cdot 0.8 \text{H}_2\text{O}$: C, 53.60; H, 5.85; N, 11.37; found: C, 53.48; H, 5.50; N, 10.98.
11		Yield: 53%. ^1H NMR (500 MHz, CDCl_3) δ : 11.54 (1H, s), 8.56 (1H, t, $J = 6.4$ Hz), 7.74 (1H, dd, $J = 8.1, 2.6$ Hz), 7.71 (1H, dd, $J = 8.6, 5.2$ Hz), 7.33 (1H, td, $J = 8.1, 2.8$ Hz), 4.83 (2H, d, $J = 7.0$ Hz), 3.97 (2H, t, $J = 6.4$ Hz), 3.16 (3H, s), 2.20-2.15 (2H, m), 1.96-1.91 (4H, m), 1.76-1.62 (6H, m). HRMS ($\text{M}+\text{H}$) calcd for $\text{C}_{21}\text{H}_{25}\text{FN}_3\text{O}_5\text{S}$: 450.1499; found: 450.1479. Anal calcd for $\text{C}_{21}\text{H}_{24}\text{FN}_3\text{O}_5\text{S}$: C, 56.11; H, 5.38; N, 9.34; found: C, 55.89; H, 5.39; N, 9.19.
12		Yield: 66%. ^1H NMR (500 MHz, CDCl_3) δ : 11.73 (1H, s), 8.71 (1H, t, $J = 6.4$ Hz), 8.45 (1H, d, $J = 3.4$ Hz), 8.18 (1H, s), 7.51 (1H, d, $J = 7.6$ Hz), 7.48-7.43 (1H, m), 7.27-7.23 (1H, m), 4.43 (2H, d, $J = 6.7$ Hz), 3.99 (2H, t, $J = 6.4$ Hz), 2.28-2.22 (2H, m), 2.00-1.92 (4H, m), 1.81-1.74 (4H, m), 1.72-1.67 (2H, m). HRMS ($\text{M}+\text{H}$) calcd for $\text{C}_{22}\text{H}_{24}\text{FN}_6\text{O}_3$: 439.1894; found: 439.1883. Anal calcd for $\text{C}_{22}\text{H}_{23}\text{FN}_6\text{O}_3$: C, 60.26; H, 5.28; N, 19.16; found: C, 60.06; H, 5.22; N, 19.09.
13		Yield: 59%. ^1H NMR (500 MHz, CDCl_3) δ : 11.90 (1H, s), 7.93 (1H, br t), 7.34-7.32 (2H, m), 7.05 (2H, t, $J = 8.5$ Hz), 4.60 (2H, d, $J = 6.4$ Hz), 3.99 (2H, t, $J = 6.4$ Hz), 3.90-3.90 (2H, m), 3.65 (2H, dt = 11.9, 1.5 Hz), 2.38 (2H, dt, $J = 13.5, 3.7$ Hz), 2.03-1.94 (4H, m), 1.52 (2H, d, $J = 13.7$ Hz). HRMS ($\text{M}-\text{H}$) calcd for $\text{C}_{20}\text{H}_{21}\text{FN}_3\text{O}_4$: 386.1516; found: 386.1499. Anal calcd for $\text{C}_{20}\text{H}_{22}\text{FN}_3\text{O}_4 \cdot 0.04 \text{H}_2\text{O} \cdot 0.2 \text{TFA}$: C, 64.79; H, 6.24; N, 10.77; found: C, 64.71; H, 6.31; N, 10.71.

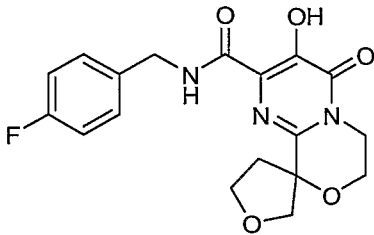
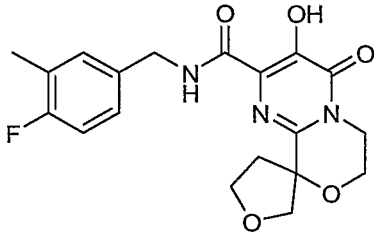
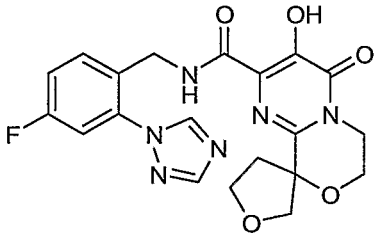
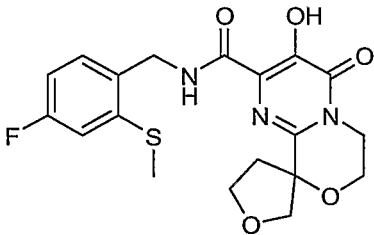
Ex.	Structure	Data
14		Yield: 79%. ^1H NMR (500 MHz, CDCl_3) δ : 12.01 (1H, s), 7.78 (1H, br t), 7.39-7.30 (5H, m), 4.63 (2H, d, $J = 6.4$ Hz), 4.03-3.96 (4H, m), 2.16-2.04 (4H, m), 1.86-1.79 (4H, m). HRMS ($\text{M}+\text{H}$) calcd for $\text{C}_{19}\text{H}_{22}\text{N}_3\text{O}_4$: 356.1610; found: 356.1616. Anal calcd for $\text{C}_{19}\text{H}_{21}\text{N}_3\text{O}_4$: C, 64.21; H, 5.95; N, 11.82; found: C, 63.98; H, 5.81; N, 11.71.
15		Yield: 85%. ^1H NMR (500 MHz, CDCl_3) δ : 11.92 (1H, s), 7.75 (1H, br t), 7.30 (2H, dd, $J = 8.5, 5.5$ Hz), 7.04 (2H, t, $J = 8.5$ Hz), 4.58 (2H, d, $J = 6.4$ Hz), 4.02-3.95 (4H, m), 2.15-2.04 (4H, m), 1.88-1.79 (4H, m). HRMS ($\text{M}+\text{H}$) calcd for $\text{C}_{19}\text{H}_{21}\text{FN}_3\text{O}_4$: 374.1516; found: 374.1506. Anal calcd for $\text{C}_{19}\text{H}_{20}\text{FN}_3\text{O}_4 \cdot 0.15 \text{H}_2\text{O}$: C, 60.09; H, 5.37; N, 11.01; F, 5.72; found: C, 59.87; H, 5.24; N, 10.90; F, 5.53.
16		Yield: 67%. ^1H NMR (500 MHz, CDCl_3) δ : 11.95 (1H, s), 7.72 (1H, br t), 7.14 (1H, d, $J = 7.0$ Hz), 7.11-7.08 (1H, m), 6.98 (1H, t, $J = 9.0$ Hz), 4.54 (2H, d, $J = 6.4$ Hz), 4.03-3.95 (4H, m), 2.27 (3H, s), 2.16-2.03 (4H, m), 1.88-1.79 (4H, m). HRMS ($\text{M}+\text{H}$) calcd for $\text{C}_{20}\text{H}_{23}\text{FN}_3\text{O}_4$: 388.1673; found: 388.1661.
17		Yield: 51%. ^1H NMR (500 MHz, CDCl_3) δ : 11.90 (1H, s), 8.76 (1H, t, $J = 6.4$ Hz), 8.44 (1H, s), 8.13 (1H, s), 7.70 (1H, dd, $J = 8.5, 6.1$ Hz), 7.21 (1H, td, $J = 8.2, 2.4$ Hz), 7.11 (1H, dd, $J = 8.4, 2.6$ Hz), 4.44 (2H, d, $J = 6.7$ Hz), 4.01-3.94 (4H, m), 2.27-2.21 (2H, m), 2.09-2.04 (2H, m), 1.93-1.88 (4H, m). HRMS ($\text{M}+\text{H}$) calcd for $\text{C}_{21}\text{H}_{22}\text{FN}_6\text{O}_4$: 441.1687; found: 441.1691. Anal calcd for $\text{C}_{21}\text{H}_{21}\text{FN}_6\text{O}_4$: N, 19.08; F, 4.31; found: N, 19.37; F, 4.56.
18		Yield: 77%. ^1H NMR (500 MHz, CDCl_3) δ : 11.84 (1H, s), 8.08 (1H, t, $J = 5.2$ Hz), 7.30 (1H, dd, $J = 8.4, 6.0$ Hz), 6.95 (1H, dd, $J = 9.5, 2.7$ Hz), 6.83 (1H, td, $J = 8.2, 2.8$ Hz), 4.60 (2H, d, $J = 6.4$ Hz), 4.01-3.94 (4H, m), 2.51 (3H, s), 2.20-2.14 (2H, m), 2.08-2.03 (2H, m), 1.88-1.82 (4H, m). HRMS ($\text{M}+\text{H}$) calcd for $\text{C}_{20}\text{H}_{23}\text{FN}_3\text{O}_4\text{S}$: 420.1393; found: 420.1383. Anal calcd for $\text{C}_{20}\text{H}_{22}\text{FN}_3\text{O}_4\text{S}$: C, 57.26; H, 5.28; N, 10.01; F, 4.52; found: C, 57.27; H, 5.31; N, 10.01; F, 4.49.

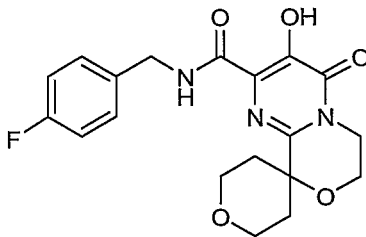
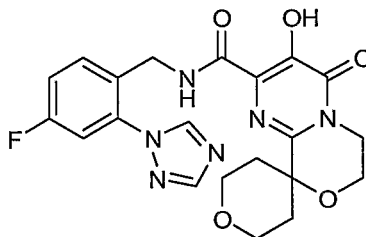
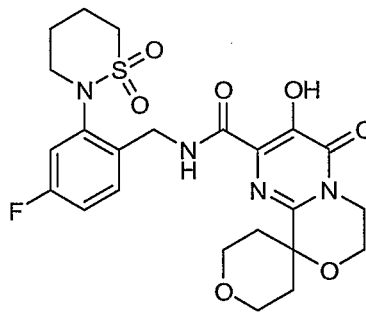
Ex.	Structure	Data
19		Yield: 83%. ^1H NMR (500 MHz, CDCl_3) δ : 12.04 (1H, s), 7.74 (1H, br t), 7.22 (2H, d, J = 7.9 Hz), 7.18 (2H, d, J = 7.9 Hz), 4.58 (2H, d, J = 6.1 Hz), 4.03-3.95 (4H, m), 2.35 (3H, s), 2.15-2.03 (4H, m), 1.87-1.79 (4H, m). HRMS ($M+H$) calcd for $\text{C}_{20}\text{H}_{24}\text{N}_3\text{O}_4$: 370.1767; found: 370.1778. Anal calcd for $\text{C}_{20}\text{H}_{23}\text{N}_3\text{O}_4$: C, 65.02; H, 6.27; N, 11.37; found: C, 64.93; H, 6.44; N, 11.32.
20		Yield: 75%. ^1H NMR (500 MHz, CDCl_3) δ : 11.90 (1H, s), 7.76 (1H, t, J = 5.4 Hz), 7.34 (2H, d, J = 7.9 Hz), 7.26 (2H, d, J = 7.9 Hz), 4.59 (2H, d, J = 6.4 Hz), 4.03-3.96 (4H, m), 2.16-2.04 (4H, m), 1.89-1.79 (4H, m). HRMS ($M+H$) calcd for $\text{C}_{19}\text{H}_{21}\text{ClN}_3\text{O}_4$: 390.1221; found: 390.1216. Anal calcd for $\text{C}_{19}\text{H}_{20}\text{ClN}_3\text{O}_4$: C, 58.54; H, 5.17; N, 10.77; found: C, 58.34; H, 5.24; N, 10.59.
21		Yield: 73%. ^1H NMR (500 MHz, CDCl_3) δ : 11.81 (1H, s), 7.79 (1H, t, J = 5.4 Hz), 7.43 (1H, d, J = 8.2 Hz), 7.41 (1H, d, J = 1.5 Hz), 7.17 (1H, dd, J = 8.2, 1.5 Hz), 4.57 (2H, d, J = 6.4 Hz), 4.03-3.96 (4H, m), 2.17-2.05 (4H, m), 1.90-1.81 (4H, m). HRMS ($M+H$) calcd for $\text{C}_{19}\text{H}_{20}\text{Cl}_2\text{N}_3\text{O}_4$: 424.0831; found: 424.0811.
22		Yield: 85%. ^1H NMR (500 MHz, CDCl_3) δ : 12.06 (1H, s), 7.74 (1H, br t), 7.13 (1H, d, J = 7.6 Hz), 7.09 (1H, s), 7.05 (1H, d, J = 7.6 Hz), 4.56 (2H, d, J = 6.1 Hz), 4.03-3.95 (4H, m), 2.26 (6H, s), 2.16-2.03 (4H, m), 1.87-1.80 (4H, m). HRMS ($M+H$) calcd for $\text{C}_{21}\text{H}_{26}\text{N}_3\text{O}_4$: 384.1923; found: 384.1937. Anal calcd for $\text{C}_{21}\text{H}_{25}\text{N}_3\text{O}_4$: C, 65.78; H, 6.57; N, 10.95; found: C, 65.58; H, 6.58; N, 10.89.
23		Yield: 84%. ^1H NMR (500 MHz, CDCl_3) δ : 12.04 (1H, s), 7.71 (1H, br t), 7.26 (2H, d, J = 8.6 Hz), 6.90 (2H, d, J = 8.6 Hz), 4.55 (2H, d, J = 6.4 Hz), 4.03-3.95 (4H, m), 3.81 (3H, s), 2.15-2.03 (4H, m), 1.87-1.79 (4H, m). HRMS ($M+H$) calcd for $\text{C}_{20}\text{H}_{24}\text{N}_3\text{O}_5$: 386.1716; found: 386.1697. Anal calcd for $\text{C}_{20}\text{H}_{23}\text{N}_3\text{O}_5 \cdot 0.11 \text{CH}_2\text{Cl}_2$: C, 61.19; H, 5.93; N, 10.64; found: C, 60.86; H, 5.98; N, 10.55.

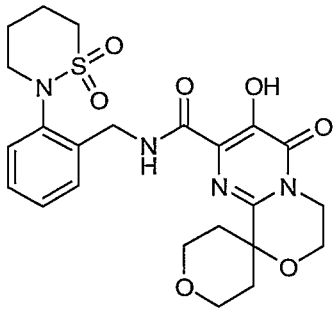
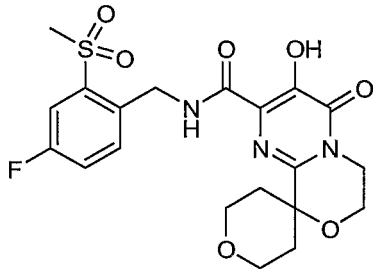
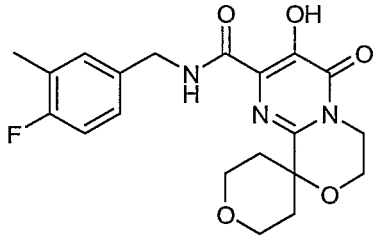
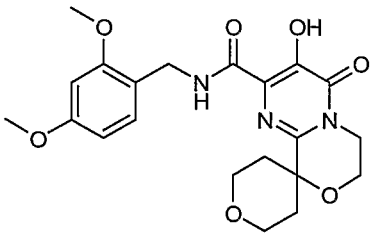
Ex.	Structure	Data
24		Yield: 78%. ^1H NMR (500 MHz, CDCl_3) δ : 11.89 (1H, s), 7.88 (1H, t, $J = 5.2$ Hz), 7.37 (1H, td, $J = 7.6$ 1.2 Hz), 7.33-7.28 (1H, m), 7.14 (1H, t, $J = 7.6$ Hz), 7.09 (1H, t, $J = 9.3$ Hz), 4.66 (2H, d, $J = 6.4$ Hz), 4.03-3.95 (4H, m), 2.19-2.13 (2H, m), 2.09-2.04 (2H, m), 1.89-1.83 (4H, m). HRMS ($\text{M}+\text{H}$) calcd for $\text{C}_{19}\text{H}_{21}\text{FN}_3\text{O}_4$: 374.1516; found: 374.1532. Anal calcd for $\text{C}_{19}\text{H}_{20}\text{FN}_3\text{O}_4 \cdot 0.05 \text{ Et}_2\text{O} \cdot 0.05 \text{ CH}_2\text{Cl}_2$: C, 60.63; H, 5.45; N, 11.02; found: C, 60.58; H, 5.33; N, 11.03.
25		Yield: 88%. ^1H NMR (500 MHz, CDCl_3) δ : 12.10 (1H, s), 8.06 (1H, t, $J = 5.6$ Hz), 7.20 (1H, d, $J = 8.2$ Hz), 6.48 (1H, d, $J = 2.4$ Hz), 6.45 (1H, dd, $J = 8.2, 2.4$ Hz), 4.51 (2H, d, $J = 6.4$ Hz), 4.01-3.95 (4H, m), 3.85 (3H, s), 3.80 (3H, s), 2.20-2.14 (2H, m), 2.09-2.04 (2H, m), 1.91-1.83 (4H, m). HRMS ($\text{M}+\text{H}$) calcd for $\text{C}_{21}\text{H}_{26}\text{N}_3\text{O}_6$: 416.1822; found: 416.1837. Anal calcd for $\text{C}_{21}\text{H}_{25}\text{N}_3\text{O}_6$: C, 60.71; H, 6.06; N, 10.11; found: C, 60.47; H, 6.10; N, 9.97.
26		Yield: 86%. ^1H NMR (500 MHz, CDCl_3) δ : 11.89 (1H, s), 7.80 (1H, br t), 7.34 (1H, q, $J = 7.6$ Hz), 7.10 (1H, d, $J = 7.6$ Hz), 7.03-6.98 (2H, m), 4.62 (2H, d, $J = 6.4$ Hz), 4.04-3.96 (4H, m), 2.17-2.05 (4H, m), 1.88-1.81 (4H, m). HRMS ($\text{M}+\text{H}$) calcd for $\text{C}_{19}\text{H}_{21}\text{FN}_3\text{O}_4$: 374.1516; found: 374.1504. Anal calcd for $\text{C}_{19}\text{H}_{20}\text{FN}_3\text{O}_4 \cdot 0.1 \text{ CH}_2\text{Cl}_2$: C, 60.07; H, 5.33; N, 11.00; found: C, 60.06; H, 5.39; N, 10.94.
27		Yield: 65%. ^1H NMR (500 MHz, CDCl_3) δ : 11.93 (1H, s), 7.76 (1H, br t), 7.17 (1H, t, $J = 7.9$ Hz), 6.99 (1H, d, $J = 7.9$ Hz), 6.97 (1H, d, $J = 10.4$ Hz), 4.57 (2H, d, $J = 6.4$ Hz), 4.03-3.96 (4H, m), 2.26 (3H, s), 2.17-2.05 (4H, m), 1.88-1.80 (4H, m). HRMS ($\text{M}+\text{H}$) calcd for $\text{C}_{20}\text{H}_{23}\text{FN}_3\text{O}_4$: 388.1673; found: 388.1665. Anal calcd for $\text{C}_{20}\text{H}_{22}\text{FN}_3\text{O}_4$: C, 62.00; H, 5.72; N, 10.84; found: C, 61.73; H, 7.72; N, 10.66.

Ex.	Structure	Data
28		Yield: 44%. ^1H NMR (500 MHz, CDCl_3) δ : 11.80 (1H, br s), 8.61 (1H, t, $J = 6.7$ Hz), 7.68 (1H, dd, $J = 8.6, 5.2$ Hz), 7.48 (1H, dd, $J = 8.4, 2.6$ Hz), 7.28-7.24 (1H, m), 4.80 (2H, d, $J = 7.0$ Hz), 4.00-3.94 (4H, m), 2.90 (6H, s), 2.24-2.18 (2H, m), 2.06-2.00 (2H, m), 1.96-1.80 (4H, m). HRMS (M+H) calcd for $\text{C}_{21}\text{H}_{26}\text{FN}_4\text{O}_6\text{S}$: 481.1557; found: 481.1561. Anal calcd for $\text{C}_{21}\text{H}_{25}\text{FN}_4\text{O}_6\text{S} \cdot 0.35 \text{CF}_3\text{CO}_2\text{H} \cdot 0.1 \text{C}_4\text{H}_{10}\text{O}$: C, 50.29; H, 5.03; N, 10.61; found: C, 50.06; H, 4.70; N, 10.51.
29		Yield: 51%. ^1H NMR (500 MHz, CDCl_3) δ : 11.84 (1H, s), 8.67 (1H, t, $J = 5.8$ Hz), 8.39 (1H, s), 8.13 (s, 1H), 7.42 (1H, dd, $J = 8.4, 2.9$ Hz), 7.34 (1H, dd, $J = 8.7, 4.2$ Hz), 7.16 (1H, td, $J = 8.1, 2.8$ Hz), 4.42 (2H, d, $J = 6.7$ Hz), 4.02-3.96 (4H, m), 2.28-2.22 (2H, m), 2.10-2.05 (2H, m), 1.94-1.88 (4H, m). HRMS (M+H) calcd for $\text{C}_{21}\text{H}_{22}\text{FN}_6\text{O}_4$: 441.1687; found: 441.1697. Anal calcd for $\text{C}_{21}\text{H}_{21}\text{FN}_6\text{O}_4$: C, 57.26; H, 4.80; N, 19.08; found: C, 57.27; H, 4.85; N, 19.07.
30		Yield: 87%. ^1H NMR (500 MHz, CDCl_3) δ : 11.92 (1H, s), 7.41 (1H, br t), 7.20-7.17 (2H, m), 7.03-7.00 (2H, m), 4.01-3.99 (2H, m), 3.96-3.94 (2H, m), 3.68 (2H, q, $J = 6.7$ Hz), 2.89 (2H, t, $J = 6.7$ Hz), 2.06-1.97 (4H, m), 1.88-1.80 (2H, m), 1.77-1.69 (2H, m). HRMS (M+H) calcd for $\text{C}_{20}\text{H}_{23}\text{FN}_3\text{O}_4$: 388.1673; found: 388.1680. Anal calcd for $\text{C}_{20}\text{H}_{22}\text{FN}_3\text{O}_4 \cdot 0.8 \text{H}_2\text{O}$: C, 60.05; H, 5.90; N, 10.50; found: C, 60.14; H, 5.60; N, 10.51.
31		Yield: 80%. ^1H NMR (500 MHz, CDCl_3) δ : 12.03 (1H, s), 7.44 (1H, br t), 7.16-7.13 (2H, m), 6.99-6.95 (2H, m), 4.03-4.01 (2H, m), 3.98-3.96 (2H, m), 3.44 (2H, q, $J = 6.7$ Hz), 2.68 (2H, t, $J = 7.6$ Hz), 2.18-2.06 (4H, m), 1.97-1.84 (6H, m). HRMS (M+H) calcd for $\text{C}_{21}\text{H}_{25}\text{FN}_3\text{O}_4$: 402.1829; found: 402.1840. Anal calcd for $\text{C}_{21}\text{H}_{24}\text{FN}_3\text{O}_4$: C, 62.83; H, 6.02; N, 10.46; found: C, 62.46; H, 6.26; N, 10.52.

Ex.	Structure	Data
32		Yield: 73%. ^1H NMR (500 MHz, CDCl_3) δ : 12.10 (1H, s), 8.55 (1H, t, $J = 6.4$ Hz), 8.29 (1H, s), 7.68 (1H, dd, $J = 8.6, 6.1$ Hz), 7.17 (1H, td, $J = 8.6, 2.8$ Hz), 7.08 (1H, dd, $J = 8.6, 2.8$ Hz), 4.47 (2H, d, $J = 6.7$ Hz), 4.02-4.00 (2H, m), 3.96-3.94 (2H, m), 2.52 (3H, s), 2.23-2.16 (2H, m), 2.09-2.04 (2H, m), 1.88-1.83 (4H, m). HRMS ($\text{M}+\text{H}$) calcd for $\text{C}_{22}\text{H}_{24}\text{FN}_6\text{O}_4$: 455.1843; found: 455.1850. Anal calcd for $\text{C}_{22}\text{H}_{23}\text{FN}_6\text{O}_4$: C, 58.14; H, 5.10; N, 18.49; found: C, 58.04; H, 4.98; N, 18.53.
33		Yield: 10%. ^1H -NMR (300 MHz, CDCl_3) δ : 11.95 (1H, s), 8.84-8.79 (1H, m), 8.41 (1H, s), 8.11 (1H, s), 7.68 (1H, dd, $J = 6.8, 2.0$ Hz), 7.51-7.42 (2H, m), 7.33 (1H, dd, $J = 7.3, 1.8$ Hz), 4.44 (2H, d, $J = 7.0$ Hz), 3.99-3.92 (4H, m), 2.27-2.18 (2H, m), 2.08-2.00 (2H, m), 1.92-1.85 (4H, m). HRMS [$\text{M}+\text{H}$] $^+$ calcd for $\text{C}_{21}\text{H}_{23}\text{N}_6\text{O}_4$: 423.1781; found: 423.1773.
34		Yield: 59% yield. ^1H -NMR (300 MHz, CDCl_3) δ : 11.83 (1H, br s), 8.26-8.22 (1H, m), 7.43 (1H, dd, $J = 8.8, 6.2$ Hz), 7.15 (1H, dd, $J = 9.1, 2.6$ Hz), 7.04 (1H, dt, $J = 8.2, 2.6$ Hz), 4.91 (1H, dd, $J = 14.1, 9.0$ Hz), 4.34 (1H, dd, $J = 14.3, 3.7$ Hz), 3.99-3.89 (4H, m), 3.86-3.77 (1H, m), 3.44-3.36 (1H, m), 3.23-3.19 (2H, m), 2.40-2.30 (2H, m), 2.21-2.10 (2H, m), 2.01-1.89 (4H, m), 1.83-1.74 (4H, m). HRMS [$\text{M}+\text{H}$] $^+$ calcd for $\text{C}_{23}\text{H}_{28}\text{N}_4\text{O}_6\text{FS}$: 507.1714; found: 507.1735. Anal calcd for $\text{C}_{23}\text{H}_{27}\text{N}_4\text{O}_6\text{FS}$: C, 54.54; H, 5.37; N, 11.06; S, 6.33; F, 3.75; found: C, 54.27; H, 5.22; N, 11.01; S, 6.14; F, 3.81.
35		Yield: 81% yield. ^1H -NMR (300 MHz, CDCl_3) δ : 12.08 (1H, s), 8.27-8.23 (1H, m), 7.46-7.41 (2H, m), 7.35-7.32 (2H, m), 4.93 (1H, dd, $J = 14.1, 9.0$ Hz), 4.40 (1H, dd, $J = 14.1, 3.5$ Hz), 4.00-3.96 (2H, m), 3.93-3.88 (2H, m), 3.86-3.81 (1H, m), 3.44-3.36 (1H, m), 3.22-3.18 (2H, m), 2.41-2.28 (2H, m), 2.21-2.11 (2H, m), 2.02-1.89 (4H, m), 1.84-1.74 (4H, m). HRMS [$\text{M}+\text{H}$] $^+$ calcd for $\text{C}_{23}\text{H}_{29}\text{N}_4\text{O}_6\text{S}$: 489.1808; found: 489.1801. Anal calcd for $\text{C}_{23}\text{H}_{28}\text{N}_4\text{O}_6\text{S}$: C, 56.54; H, 5.78; N, 11.47; found: C, 56.63; H, 5.48; N, 11.37.

Ex.	Structure	Data
36		Yield: 65%. ^1H NMR (500 MHz, CDCl_3) δ : 12.10 (1H, s), 7.74 (1H, br t), 7.30 (2H, dd, $J = 8.5, 5.2$ Hz), 7.04 (2H, t, $J = 8.5$ Hz), 4.62-4.53 (2H, m), 4.14-3.99 (8H, m), 2.51-2.45 (1H, m), 2.36-2.31 (1H, m). HRMS ($\text{M}+\text{H}$) calcd for $\text{C}_{18}\text{H}_{19}\text{FN}_3\text{O}_5$; found: . Anal calcd for $\text{C}_{18}\text{H}_{18}\text{FN}_3\text{O}_5$: C, 57.59; H, 4.83; N, 11.19; F, 5.06; found: C, 57.95; H, 4.96; N, 10.95; F, 5.43.
37		Yield: 68%. ^1H NMR (500 MHz, CDCl_3) δ : 12.13 (1H, s), 7.71 (1H, br t), 7.14-7.08 (2H, m), 6.97 (1H, t, $J = 8.8$ Hz), 4.57-4.49 (2H, m), 4.14-3.99 (8H, m), 2.51-2.44 (1H, m), 2.36-2.31 (1H, m), 2.27 (3H, s). HRMS ($\text{M}+\text{H}$) calcd for $\text{C}_{19}\text{H}_{21}\text{FN}_3\text{O}_5$: 390.1465; found: 390.1451. Anal calcd for $\text{C}_{19}\text{H}_{20}\text{FN}_3\text{O}_5$: C, 58.60; H, 5.17; N, 10.79; F, 4.87; found: C, 58.62; H, 5.36; N, 10.77; F, 4.95.
38		Yield: 52%. ^1H NMR (500 MHz, CDCl_3) δ : 11.908 (1H, s), 8.92 (1H, br t), 8.43 (1H, s), 8.26 (1H, s), 7.69 (1H, dd, $J = 8.5, 5.8$ Hz), 7.21 (1H, td, $J = 8.2, 2.4$ Hz), 7.10 (1H, dd, $J = 8.5, 2.4$ Hz), 4.51-4.35 (2H, m), 4.26-3.97 (8H, m), 2.59-2.53 (1H, m), 2.36-2.31 (1H, m). HRMS ($\text{M}+\text{H}$) calcd for $\text{C}_{20}\text{H}_{20}\text{FN}_6\text{O}_5$: 443.1479; found: 443.1495. Anal calcd for $\text{C}_{20}\text{H}_{19}\text{FN}_6\text{O}_5$: C, 54.29; H, 4.32; N, 18.99; F, 4.29; found: C, 54.26; H, 4.44; N, 19.01; F, 4.38.
39		Yield: 63%. ^1H NMR (500 MHz, CDCl_3) δ : 12.01 (1H, s), 8.03 (1H, br t), 7.30-7.24 (1H, m), 6.99-6.94 (1H, m), 6.87-6.81 (1H, m), 4.64-4.59 (2H, m), 4.14-3.99 (8H, m), 2.55-2.51 (1H, m), 2.51 (3H, s), 2.38-2.31 (1H, m). HRMS ($\text{M}+\text{H}$) calcd for $\text{C}_{19}\text{H}_{21}\text{FN}_3\text{O}_5\text{S}$: 422.1186; found: 422.1165. Anal calcd for $\text{C}_{19}\text{H}_{21}\text{FN}_3\text{O}_5\text{S}$: C, 54.14; H, 4.78; N, 9.97; found: C, 54.22; H, 5.07; N, 9.90.

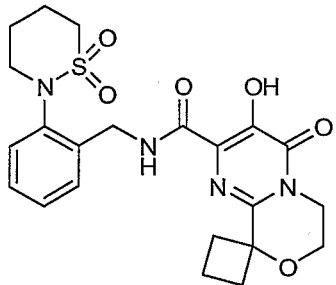
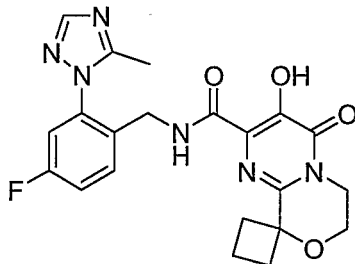
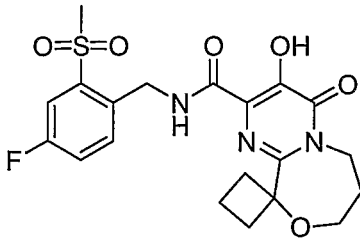
Ex.	Structure	Data
40		Yield: 28%. $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ : 12.07 (1H, s), 7.81 (1H, t, $J = 6.0$ Hz), 7.32 (2H, dd, $J = 8.5, 5.5$ Hz), 7.06 (2H, t, $J = 8.7$ Hz), 4.58 (2H, d, $J = 6.4$ Hz), 4.05-4.01 (4H, m), 3.84 (2H, dd, $J = 11.4, 5.3$ Hz), 3.77 (2H, t, $J = 11.3$ Hz), 2.30 (2H, dt, $J = 13.3, 5.2$ Hz), 1.79 (2H, d, $J = 13.7$ Hz). HRMS $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{19}\text{H}_{21}\text{N}_3\text{O}_5\text{F}$: 390.14653; found: 390.1465. Anal calcd for $\text{C}_{19}\text{H}_{20}\text{N}_3\text{O}_5\text{F}$: C, 58.60; H, 5.17; N, 10.79; F, 4.87; found: C, 58.70; H, 5.26; N, 10.80; F, 4.99.
41		Yield: 30%. $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ : 11.86 (1H, s), 9.12 (1H, t, $J = 5.6$ Hz), 8.46 (1H, s), 8.39 (1H, s), 7.68 (1H, dd, $J = 8.2, 6.1$ Hz), 7.21 (1H, dt, $J = 8.2, 2.1$ Hz), 7.10 (1H, dd, $J = 8.4, 2.0$ Hz), 4.45 (2H, dd, $J = 6.7$ Hz), 4.02 (4H, s), 3.90 (2H, dd, $J = 11.3, 4.6$ Hz), 3.79 (2H, t, $J = 11.7$ Hz), 2.44 (2H, dt, $J = 13.1, 4.9$ Hz), 1.80 (2H, d, $J = 13.4$ Hz). HRMS $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{21}\text{H}_{22}\text{N}_6\text{O}_5\text{F}$: 457.16358; found: 457.1639. Anal calcd for $\text{C}_{21}\text{H}_{21}\text{N}_6\text{O}_5\text{F}$: C, 55.26; H, 4.63; N, 18.41; F, 4.16; found: C, 54.99; H, 4.54; N, 18.38; F, 4.08.
42		Yield: 53%. $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ : 12.12 (1H, s), 8.25-8.23 (1H, m), 7.48 (1H, q, $J = 8.5, 6.1$ Hz), 7.21 (1H, dd, $J = 9.0, 2.6$ Hz), 7.08 (1H, dt, $J = 8.2, 2.5$ Hz), 4.90 (1H, dd, $J = 14.2, 8.4$ Hz), 4.43 (1H, dd, $J = 14.0, 4.3$ Hz), 4.01 (4H, s), 3.86-3.71 (4H, m), 3.45-3.42 (1H, m), 3.32 (1H, dt, $J = 13.2, 4.4$ Hz), 3.28-3.22 (1H, m), 2.47-2.29 (4H, m), 2.00-1.93 (2H, m), 1.72 (2H, t, $J = 15.2$ Hz). HRMS $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{23}\text{H}_{28}\text{N}_6\text{O}_7\text{FS}$: 523.1663; found: 523.1666. Anal calcd for $\text{C}_{23}\text{H}_{27}\text{N}_6\text{O}_7\text{FS} \cdot 0.5 \text{H}_2\text{O}$: C, 51.97; H, 5.31; N, 10.54; F, 3.57; S, 6.03; found: C, 51.84; H, 4.96; N, 10.28; F, 3.62; S, 6.01.

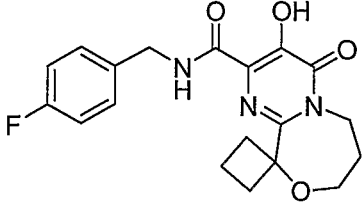
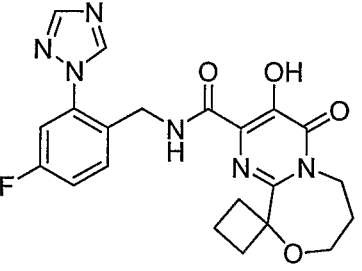
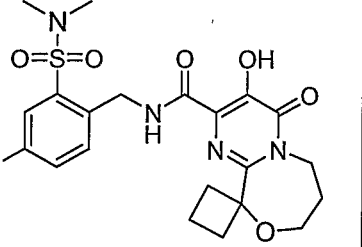
Ex.	Structure	Data
43		Yield: 65%. $^1\text{H-NMR}$ (300 MHz, CDCl_3 /1 drop MeOD) δ : 8.28-8.24 (1H, m), 7.46-7.43 (2H, m), 7.35-7.32 (2H, m), 4.89 (1H, dd, $J = 14.3$, 8.4 Hz), 4.45 (1H, dd, $J = 14.3$, 4.4 Hz), 3.97 (4H, s), 3.89-3.65 (5H, m), 3.43-3.36 (1H, m), 3.33-3.16 (2H, m), 2.46-2.24 (4H, m), 1.96-1.88 (2H, m), 1.73-1.65 (2H, m). HRMS $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{23}\text{H}_{29}\text{N}_4\text{O}_7\text{S}$: 505.1757; found: 505.1761. Anal calcd for $\text{C}_{23}\text{H}_{28}\text{N}_4\text{O}_7\text{S}$: C, 54.75; H, 5.59; N, 11.10; S, 6.35; found: C, 55.03; H, 5.29; N, 11.06; S, 6.18.
44		Yield: 70%. $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 11.80 (1H, s), 8.50 (1H, t, $J = 6.6$ Hz), 7.74 (1H, dd $J = 8.1$, 2.9 Hz), 7.65 (1H, dd, $J = 8.6$, 5.3 Hz), 7.31 (1H, dt, $J = 8.0$, 3.2 Hz), 4.82 (2H, d, $J = 6.9$ Hz), 3.99 (4H, s), 3.84 (2H, dd, $J = 11.5$, 4.9 Hz), 3.74 (2H, td, $J = 11.6$, 1.3 Hz), 3.18 (3H, s), 2.31 (2H, td, $J = 13.2$, 5.5 Hz), 1.74 (2H, d, $J = 13.2$ Hz). HRMS $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{20}\text{H}_{23}\text{N}_3\text{O}_7\text{SF}$: 468.1241; found: 468.1237. Anal calcd for $\text{C}_{20}\text{H}_{22}\text{N}_3\text{O}_7\text{SF}$: C, 51.38; H, 4.74; N, 8.98; S, 6.86; F, 4.06; found: C, 51.25; H, 4.62; N, 8.81; S, 6.82; F, 4.18.
45		Yield: 19%. $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 12.08 (1H, s), 7.75 (1H, s, $J = 5.8$ Hz), 7.15-7.08 (2H, m), 6.96 (1H, t, $J = 9.0$ Hz), 4.51 (2H, d, $J = 6.2$ Hz), 4.00 (4H, s), 3.85-3.70 (4H, m), 2.32-2.22 (2H, m), 2.26 (3H, d, $J = 1.8$ Hz), 1.76 (2H, d, $J = 13.5$ Hz). HRMS $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{20}\text{H}_{23}\text{N}_3\text{O}_5\text{F}$: 404.1622; found: 404.1615.
46		Yield: 39%. $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 12.18 (1H, s), 8.12 (1H, t, $J = 6.0$ Hz), 7.19 (1H, d, $J = 8.0$ Hz), 6.48-6.41 (2H, m), 4.50 (2H, d, $J = 6.2$ Hz), 3.99 (3H, s), 3.88 (3H, s), 3.86-3.71 (4H, m), 3.78 (4H, s), 2.27 (2H, td, $J = 13.0$, 5.6 Hz), 1.76 (2H, d, $J = 12.8$ Hz). HRMS $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{21}\text{H}_{26}\text{N}_3\text{O}_7$: 432.1771; found: 432.1771. Anal calcd for $\text{C}_{21}\text{H}_{25}\text{N}_3\text{O}_7$: C, 58.46; H, 5.84; N, 9.74; found: C, 58.22; H, 5.89; N, 9.69.

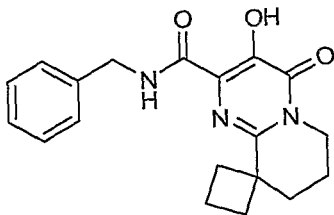
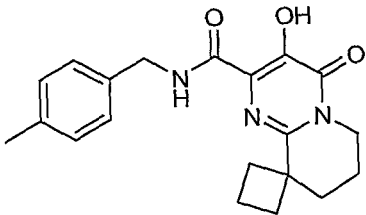
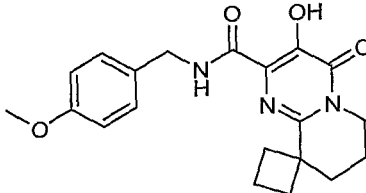
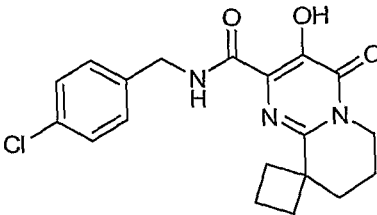
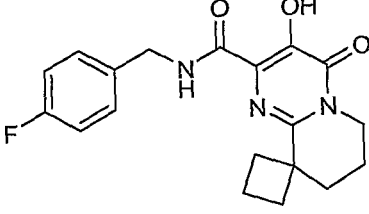
Ex.	Structure	Data
47		Yield: 44%. $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 11.91 (1H, s), 8.52 (1H, t, $J = 6.6$ Hz), 7.63 (1H, dd, $J = 8.4, 5.5$ Hz), 7.47 (1H, dd, $J = 8.4, 2.9$ Hz), 7.27-7.22 (1H, m), 4.81 (2H, d, $J = 6.9$ Hz), 3.98 (4H, s), 3.85-3.70 (4H, m), 2.90 (6H, s), 2.31 (2H, td, $J = 13.0, 5.2$ Hz), 1.73 (2H, d, $J = 13.5$ Hz). HRMS $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{21}\text{H}_{26}\text{N}_4\text{O}_7\text{FS}$: 497.1506; found: 497.1497. Anal calcd for $\text{C}_{21}\text{H}_{25}\text{N}_4\text{O}_7\text{FS}$: C, 50.80; H, 5.07; N, 11.28; S, 6.45; F, 3.82; found: C, 50.59; H, 4.99; N, 11.01; S, 6.19; F, 4.03.
48		Yield: 54%. $^1\text{H-NMR}$ (500 MHz, CDCl_3) δ : 12.20 (1H, s), 7.76 (1H, t, $J = 5.3$ Hz), 7.14-7.11 (2H, m), 7.08 (1H, d, $J = 7.6$ Hz), 4.54 (2H, d, $J = 6.1$ Hz), 4.04-4.01 (4H, m), 3.83 (2H, dd, $J = 11.4, 5.0$ Hz), 3.77 (2H, t, $J = 11.4$ Hz), 2.32-2.28 (2H, m), 2.26 (6H, d, $J = 5.8$ Hz), 1.78 (2H, d, $J = 13.4$ Hz). HRMS $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{21}\text{H}_{26}\text{N}_3\text{O}_5$: 400.1872; found: 400.1869. Anal calcd for $\text{C}_{21}\text{H}_{25}\text{N}_3\text{O}_5$: C, 63.14; H, 6.30; N, 10.52; found: C, 62.39; H, 6.01; N, 10.23.
49		Yield: 59%. $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 11.80 (1H, s), 8.83 (1H, t, $J = 6.2$ Hz), 8.20 (1H, s), 7.63 (1H, dd, $J = 8.6, 6.0$ Hz), 7.20 (1H, dd, $J = 8.6, 2.4$ Hz), 6.99 (1H, dd, $J = 8.4, 2.6$ Hz), 4.27 (2H, d, $J = 6.6$ Hz), 3.99 (4H, s), 3.87 (2H, dd, $J = 11.3, 4.4$ Hz), 3.76 (2H, t, $J = 11.7$ Hz), 2.45 (3H, s), 2.48-2.38 (2H, m), 1.78 (2H, d, $J = 13.5$ Hz). HRMS $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{22}\text{H}_{24}\text{N}_6\text{O}_5\text{F}$: 471.1792; found: 471.1786. Anal calcd for $\text{C}_{22}\text{H}_{23}\text{N}_6\text{O}_5\text{F}$: C, 56.16; H, 4.92; N, 17.86; F, 4.03; found: C, 55.88; H, 5.02; N, 17.74; F, 3.79.
50		Yield: 35%. $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 12.11 (1H, s), 8.78 (1H, t, $J = 7.3$ Hz), 8.28 (1H, s), 7.66 (1H, dd, $J = 8.6, 6.0$ Hz), 7.14 (1H, td, $J = 8.2, 2.7$ Hz), 7.06 (1H, dd, $J = 8.4, 2.6$ Hz), 4.45 (2H, d, $J = 6.6$ Hz), 3.99 (4H, s), 3.82-3.71 (4H, m), 2.59 (3H, s), 2.39-2.29 (2H, m), 1.75 (2H, d, $J = 14.3$ Hz). HRMS (M+H) calcd for $\text{C}_{22}\text{H}_{24}\text{N}_6\text{O}_5\text{F}$: 471.1792; found: 471.1812. Anal calcd for $\text{C}_{22}\text{H}_{24}\text{N}_6\text{O}_5\text{F} \cdot 0.2 \text{H}_2\text{O}$: C, 55.74; H, 4.98; N, 17.73; F, 4.01; found: C, 55.60; H, 4.92; N, 17.85; F, 3.84.

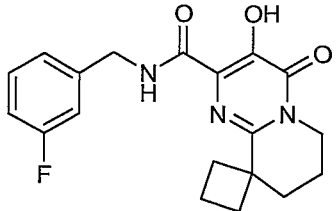
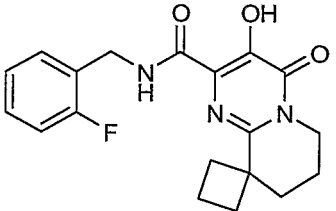
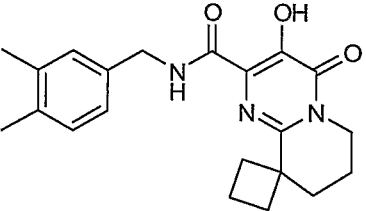
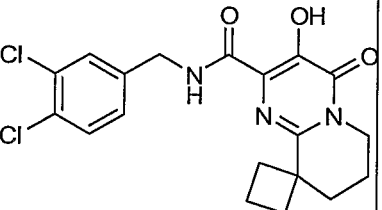
Ex.	Structure	Data
51		Yield: 34%. ¹ H NMR (500 MHz, CDCl ₃) δ: 12.01 (1H, s), 8.95 (1H, t, <i>J</i> = 6.3 Hz), 8.46 (1H, s), 8.15 (1H, s), 7.73 (1H, dd, <i>J</i> = 8.6, 6.1 Hz), 7.21 (1H, td, <i>J</i> = 8.2, 2.6 Hz), 7.12 (1H, dd, <i>J</i> = 8.6, 2.4 Hz), 4.47 (2H, d, <i>J</i> = 6.7 Hz), 3.96 (4H, s), 2.67-2.75 (2H, m), 2.32-2.40 (2H, m), 2.15-2.24 (1H, m), 2.08 (1H, m). HRMS (M+H) calcd for C ₂₀ H ₂₀ N ₆ O ₄ F: 427.1530; found: 427.1540.
52		Yield: 27%. ¹ H NMR (500 MHz, CDCl ₃) δ: 12.00 (1H, s), 7.82-7.90 (1H, m), 7.32 (2H, dd, <i>J</i> = 9, 5 Hz), 7.02-7.08 (2H, m), 4.61 (2H, d, 6 Hz), 3.97 (4H, ddd, 14, 8, 3 Hz), 2.60-2.66 (2H, m), 2.29-2.36 (2H, m), 2.01-2.10 (1H, m), 1.90-1.99 (1H, m). ¹³ C NMR (126 MHz, CDCl ₃) δ: 168.39, 163.46, 161.50, 157.66, 150.60, 146.85, 133.20, 133.17, 129.42, 129.36, 125.40, 116.02, 115.84, 78.73, 58.62, 42.53, 34.74, 14.13. HRMS (M+H) calcd for C ₁₈ H ₁₉ N ₃ O ₄ F: 360.1360; found: 360.1350.
53		Yield: 43%. ¹ H NMR (500 MHz, CDCl ₃) δ: 11.81 (1H, s), 8.68 (1H, t, <i>J</i> = 7 Hz), 7.71-7.77 (2H, m), 7.35 (1H, td, 8, 3 Hz), 4.84 (2H, d, 7 Hz), 3.93-3.95 (4H, m), 3.18 (3H, s), 2.62-2.68 (2H, m), 2.29-2.36 (2H, m), 2.13-2.19 (1H, m), 2.01-2.08 (1H, m). ¹³ C NMR (126 MHz, CDCl ₃) δ: 168.22, 163.16, 161.14, 157.70, 150.86, 146.63, 140.77, 140.72, 135.31, 135.25, 132.83, 132.80, 125.57, 121.69, 121.53, 117.65, 117.45, 78.69, 58.51, 45.18, 42.53, 40.34, 34.84, 13.59. HRMS (M+H) calcd for C ₁₉ H ₂₁ FN ₃ O ₆ S: 438.1135, found 438.1149.

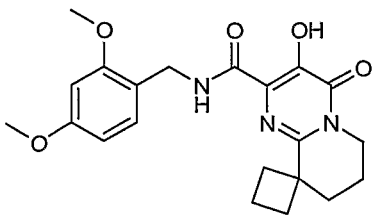
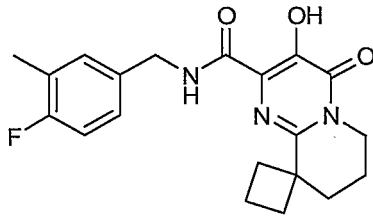
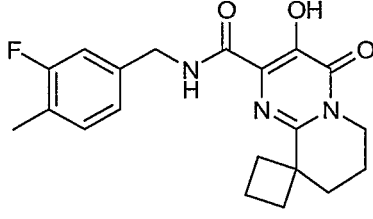
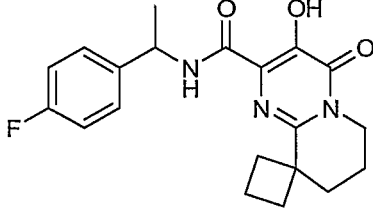
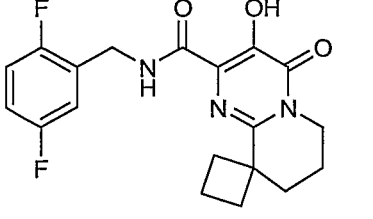
Ex.	Structure	Data
54		Yield: 56%. ^1H NMR (500 MHz, CDCl_3) δ: 11.91 (1H, s), 8.73 (1H, t, $J = 6.7$ Hz), 7.71 (1H, dd, $J = 8.4, 5.3$ Hz), 7.49 (1H, dd, $J = 8.4, 2.6$ Hz), 7.25-7.29 (1H, m), 4.83 (2H, d, $J = 7.0$ Hz), 3.94 (4H, s), 2.90 (6H, s), 2.64-2.70 (2H, m), 2.28-2.35 (2H, m), 2.12-2.21 (1H, m), 1.99-2.08 (1H, m). ^{13}C NMR (126 MHz, CDCl_3) δ: 168.09, 162.72, 160.72, 157.75, 150.67, 146.59, 138.58, 138.53, 135.31, 135.25, 132.70, 132.67, 125.73, 120.40, 120.23, 116.86, 116.66, 78.74, 58.53, 42.50, 40.34, 37.61, 34.81, 13.58. HRMS ($\text{M}+\text{H}$) calcd for $\text{C}_{20}\text{H}_{24}\text{N}_4\text{O}_6\text{FS}$ 467.1401, found 467.1418. Anal. calcd for $\text{C}_{20}\text{H}_{23}\text{N}_4\text{O}_6\text{FS}$: C 51.49, H 4.97, N 12.01, F 4.07, S 6.87; found: C 51.27, H 4.98, N 12.17, F 4.11, S 6.86.
55		Yield: 73%. ^1H NMR (500 MHz, CDCl_3) δ: 12.16 (1H, s), 8.33-8.39 (1H, m), 7.49 (1H, dd, $J = 8.7, 6.3$ Hz), 7.17 (1H, dd, $J = 9.0, 2.6$ Hz), 7.07 (1H, td, $J = 8.2, 2.6$ Hz), 4.97 (1H, dd, $J = 14.0, 8.9$ Hz), 4.40 (1H, dd, $J = 14.3, 3.7$ Hz), 3.92-3.98 (4H, m), 3.81-3.88 (1H, m), 3.44 (1H, dt, $J = 12.6, 3.6$ Hz), 3.23-3.28 (2H, m), 2.64-2.70 (2H, m), 2.32-2.42 (2H, m), 2.20-2.29 (2H, m), 1.98-2.06 (2H, m), 1.88-1.98 (2H, m). ^{13}C NMR (126 MHz, CDCl_3) δ: 168.28, 163.49, 161.50, 157.79, 150.47, 146.69, 139.89, 139.82, 133.17, 132.16, 132.08, 125.81, 116.64, 116.47, 115.15, 114.97, 79.12, 58.57, 54.17, 51.07, 42.54, 38.53, 34.58, 34.52, 24.97, 24.24, 14.00. HRMS ($\text{M}+\text{H}$) calcd for $\text{C}_{22}\text{H}_{26}\text{N}_4\text{O}_6\text{FS}$ 493.1557; found 493.1549. Anal. calcd for $\text{C}_{22}\text{H}_{25}\text{N}_4\text{O}_6\text{FS}$: C 53.65, H 5.12, N 11.38, F 3.86, S 6.51; found: C 53.73, H 4.91, N 11.06, F 3.55, S 6.42.

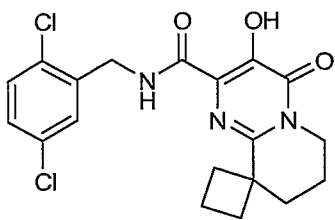
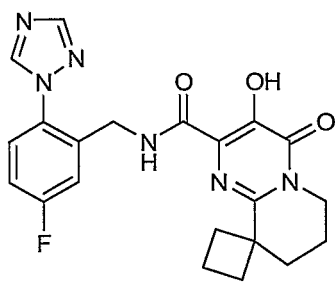
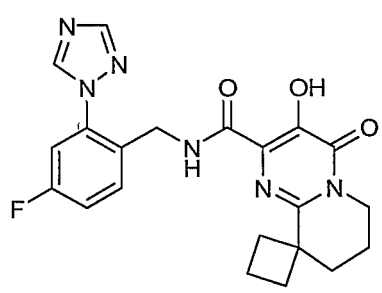
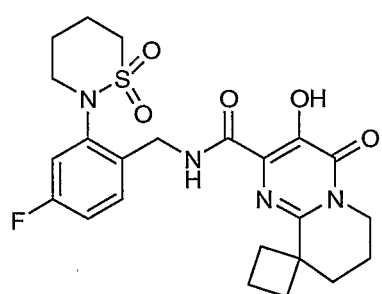
Ex.	Structure	Data
56		Yield: 66%. ¹ H NMR (500 MHz, CDCl ₃) δ: 12.15-12.29 (1H, br s), 8.32-8.40 (1H, m), 7.47-7.52 (1H, m), 7.42-7.47 (1H, m), 7.33-7.39 (2H, m), 4.99 (1H, dd, <i>J</i> = 14.0, 8.9 Hz), 4.47 (1H, dd, <i>J</i> = 14.3, 3.7 Hz), 3.92-3.98 (4H, m), 3.84-3.92 (1H, m), 3.41-3.47 (1H, m), 3.22-3.28 (2H, m), 2.64-2.71 (2H, m), 2.37-2.46 (1H, m), 2.31-2.37 (1H, m), 2.19-2.29 (2H, m), 1.98-2.06 (2H, m), 1.89-1.98 (2H, m). ¹³ C NMR (126 MHz, CDCl ₃) δ: 168.26, 157.82, 150.40, 146.68, 138.82, 137.01, 130.80, 129.46, 129.32, 127.72, 125.90, 79.15, 58.58, 54.15, 51.05, 42.53, 39.17, 34.58, 34.51, 25.05, 24.34, 14.03. HRMS (M+H) calcd for C ₂₂ H ₂₇ N ₄ O ₆ S 475.1651; found 475.1665. Anal. calcd for C ₂₂ H ₂₆ N ₄ O ₆ S: C 55.68, H 5.52, N 11.81, S 6.76; found: C 55.53, H 5.36, N 11.77, S 6.61.
57		Yield: 55%. ¹ H NMR (500 MHz, CDCl ₃) δ: 11.93 (1H, s), 8.61 (1H, br), 7.98 (1H, s), 7.70 (1H, dd, <i>J</i> = 8.5, 5.8 Hz), 7.22-7.26 (1H, m), 7.02 (1H, dd, <i>J</i> = 8.4, 2.6 Hz), 4.32 (2H, d, <i>J</i> = 6.7 Hz), 3.94-3.97 (4H, m), 2.72 (2H, ddd, <i>J</i> = 12.7, 9.2, 5.5 Hz), 2.48 (3H, s), 2.36 (2H, ddd, <i>J</i> = 12.5, 10.1, 7.3 Hz), 2.15-2.23 (1H, m), 2.05-2.14 (1H, m). ¹³ C NMR (126 MHz, CDCl ₃) δ: 168.13, 163.04, 161.04, 157.64, 153.70, 151.42, 150.47, 146.83, 137.25, 137.17, 133.57, 133.50, 130.89, 130.86, 125.58, 117.61, 117.45, 114.43, 114.24, 78.78, 65.84, 58.62, 42.44, 38.82, 34.75, 15.29, 13.83, 12.68. HRMS (M+H) calcd for C ₂₁ H ₂₂ N ₆ O ₄ F: 441.1687; found: 441.1692.
58		Yield: 43%. ¹ H NMR (500 MHz, CDCl ₃) δ: 11.90 (1H, br s), 8.62 (1H, t, 6.7 Hz), 7.74 (1H, dd, <i>J</i> = 7.9, 2.8 Hz), 7.71 (1H, dd, <i>J</i> = 8.6, 5.2 Hz), 7.34 (1H, dt, <i>J</i> = 8.0, 2.6 Hz), 4.83 (2H, d, <i>J</i> = 6.7 Hz), 4.36 (2H, br), 3.89 (2H, t, <i>J</i> = 5.7 Hz), 3.17 (3H, s), 2.69-2.79 (2H, br), 2.37-2.46 (2H, m), 1.85-1.94 (1H, m), 1.79-.85 (2H, m), 1.63-1.73 (1H, m). ¹³ C NMR (125.77 MHz, CDCl ₃) δ: 168.34, 163.12, 161.11, 158.52, 151.12, 147.55, 140.72, 140.67, 135.12, 135.05, 132.86, 132.83, 124.42, 121.66, 121.49, 117.61, 117.41, 82.32, 64.43, 45.17, 40.80, 40.25, 32.02, 28.59, 12.79. HRMS (M+H) calcd for C ₂₀ H ₂₃ FN ₃ O ₆ S: 452.1292, found 452.1299.

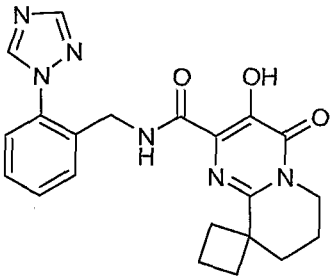
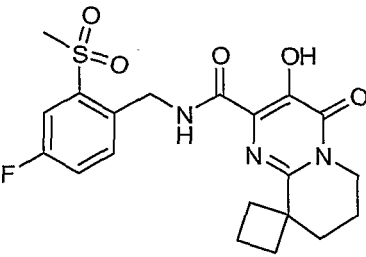
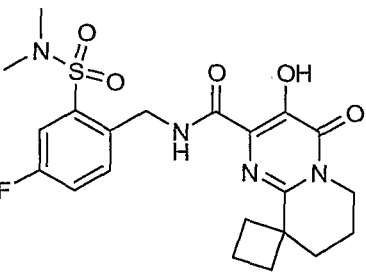
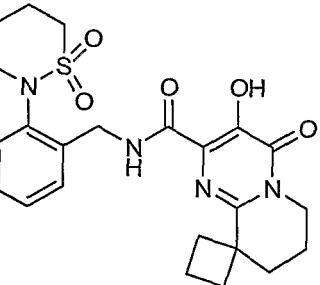
Ex.	Structure	Data
59		Yield: 52%. ^1H NMR (500 MHz, CDCl_3) δ : 12.09 (1H, s), 7.82 (1H, br t), 7.31 (2H, dd, J = 8.1, 5.6 Hz), 7.05 (2H, t, J = 8.5 Hz), 4.59 (2H, d, J = 6.1 Hz), 4.39 (2H, br), 3.92 (2H, t, J = 5.5 Hz), 2.63-2.71 (2H, br), 2.38-2.46 (2H, m), 1.89 (1H, td, J = 10.0, 5.6 Hz), 1.82-1.87 (2H, m), 1.60-1.69 (1H, m). ^{13}C NMR (126 MHz, CDCl_3) δ : 168.48, 163.46, 161.49, 158.45, 150.94, 147.73, 133.15, 133.12, 129.45, 129.39, 124.27, 115.99, 115.83, 82.11, 64.59, 42.49, 40.81, 31.88, 28.67, 12.85. HRMS ($\text{M}+\text{H}$) calcd for $\text{C}_{19}\text{H}_{21}\text{FN}_3\text{O}_4$: 374.1516; found: 374.1515.
60		Yield: 18%. ^1H NMR (500 MHz, CDCl_3) δ : 12.10 (1H, s), 9.02 (1H, t, J = 6.4 Hz), 8.46 (1H, s), 8.13 (1H, s), 7.71 (1H, dd, J = 8.5, 5.8 Hz), 7.21 (1H, td, J = 8.2, 2.7 Hz), 7.11 (1H, dd, J = 8.4, 2.6 Hz), 4.45 (2H, d, J = 7.0 Hz), 4.38 (2H, br), 3.89 (2H, t, J = 5.6 Hz), 2.82 (2H, br), 2.41-2.48 (2H, m), 1.87-1.95 (1H, m), 1.83 (2H, ddd, J = 10.8, 5.6, 5.5 Hz), 1.69-1.78 (1H, m). ^{13}C NMR (126 MHz, CDCl_3) δ : 168.10, 163.20, 161.20, 158.53, 152.73, 150.74, 147.62, 143.85, 136.97, 136.89, 134.46, 134.38, 128.65, 128.61, 124.63, 117.14, 116.98, 112.38, 112.19, 82.35, 64.46, 40.71, 39.11, 32.10, 28.61, 12.71. HRMS ($\text{M}+\text{H}$) calcd for $\text{C}_{21}\text{H}_{22}\text{FN}_6\text{O}_4$: 441.1687, found: 441.1695.
61		Yield: 33%. ^1H NMR (500 MHz, CDCl_3) δ : 12.02 (1H, br s), 8.64 (1H, t, J = 6.6 Hz), 7.69 (1H, dd, J = 8.5, 5.5 Hz), 7.49 (1H, dd, J = 8.2, 2.7 Hz), 7.24-7.29 (1H, m), 4.82 (2H, d, J = 6.7 Hz), 4.36 (2H, br), 3.88 (2H, t, J = 5.5 Hz), 2.89 (6H, s), 2.74 (2H, m), 2.37-2.44 (2H, m), 1.85-1.92 (1H, m), 1.82 (2H, dt, J = 11.0, 5.5 Hz), 1.65-1.74 (1H, m). ^{13}C NMR (126 MHz, CDCl_3) δ : 168.21, 162.69, 160.68, 158.54, 150.96, 147.55, 138.56, 138.50, 135.15, 135.09, 132.72, 132.69, 124.57, 120.38, 120.22, 116.84, 116.64, 82.37, 64.39, 40.71, 40.22, 37.58, 32.09, 28.59, 12.77. HRMS ($\text{M}+\text{H}$) calcd for $\text{C}_{21}\text{H}_{26}\text{FN}_4\text{O}_6\text{FS}$ 481.1557, found 481.1555. Anal. calcd for $\text{C}_{21}\text{H}_{25}\text{N}_4\text{O}_6\text{FS}$: C 52.49, H 5.24, N 11.66, F 3.95, S 6.67; found: C 52.22, H 5.09, N 11.43, F 3.93, S 6.60.

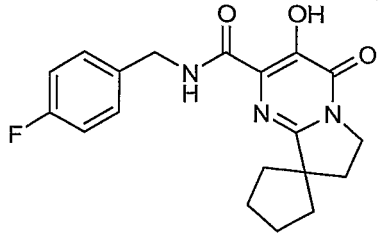
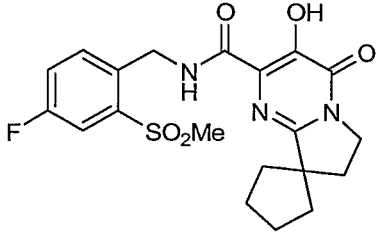
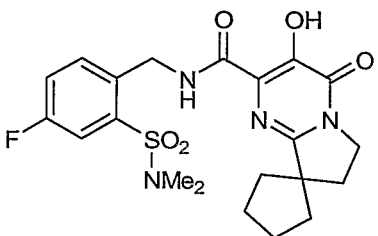
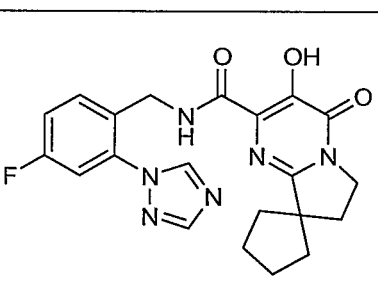
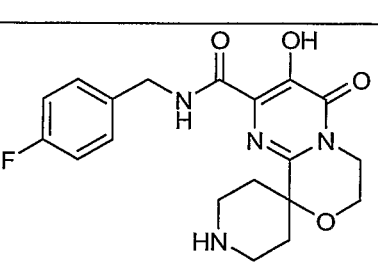
Ex.	Structure	Data
62		Yield: 82%. ^1H NMR (500 MHz, CDCl_3) δ : 11.90 (1H, s), 8.03 (1H, br t), 7.40-7.30 (5H, m), 4.67 (2H, d, $J = 6.4$ Hz), 3.96 (2H, t, $J = 6.4$ Hz), 2.63-2.57 (2H, m), 2.07-1.91 (8H, m). HRMS (M+H) calcd for $\text{C}_{19}\text{H}_{22}\text{N}_3\text{O}_3$: 340.1661; found: 340.1652. Anal calcd for $\text{C}_{19}\text{H}_{21}\text{N}_3\text{O}_3$: C, 67.24; H, 6.23; N, 12.38; found: C, 66.85; H, 6.14; N, 12.31.
63		Yield: 78%. ^1H NMR (500 MHz, CDCl_3) δ : 11.93 (1H, s), 7.99 (1H, br t), 7.25 (2H, d, $J = 6.7$ Hz), 7.18 (2H, d, $J = 7.6$ Hz), 4.62 (2H, d, $J = 6.1$ Hz), 3.96 (2H, t, $J = 6.3$ Hz), 2.62-2.56 (2H, m), 2.35 (3H, s), 2.07-1.90 (8H, m). HRMS (M+H) calcd for $\text{C}_{20}\text{H}_{24}\text{N}_3\text{O}_3$: 354.1818; found: 354.1823. Anal calcd for $\text{C}_{20}\text{H}_{23}\text{N}_3\text{O}_3$: C, 67.97; H, 6.55; N, 11.89; found: C, 67.81; H, 6.84; N, 11.94.
64		Yield: 76%. ^1H NMR (500 MHz, CDCl_3) δ : 11.93 (1H, s), 7.96 (1H, t, $J = 5.2$ Hz), 7.29 (2H, d, $J = 8.5$ Hz), 6.90 (2H, d, $J = 8.5$ Hz), 4.59 (2H, d, $J = 6.6$ Hz), 3.96 (2H, t, $J = 6.4$ Hz), 3.81 (3H, s), 2.62-2.56 (2H, m), 2.07-1.90 (8H, m). HRMS (M+H) calcd for $\text{C}_{20}\text{H}_{24}\text{N}_3\text{O}_4$: 370.1767; found: 370.1780. Anal calcd for $\text{C}_{20}\text{H}_{23}\text{N}_3\text{O}_4$: C, 65.02; H, 6.27; N, 11.37; found: C, 64.94; H, 6.53; N, 11.46.
65		Yield: 74%. ^1H NMR (500 MHz, CDCl_3) δ : 11.79 (1H, s), 8.02 (1H, br t), 7.34 (2H, d, $J = 8.6$ Hz), 7.29 (2H, d, $J = 8.6$ Hz), 4.63 (2H, d, $J = 6.4$ Hz), 3.96 (2H, t, $J = 6.4$ Hz), 2.63-2.57 (2H, m), 2.08-1.91 (8H, m). HRMS (M+H) calcd for $\text{C}_{19}\text{H}_{21}\text{ClN}_3\text{O}_3$: 374.1271; found: 374.1287. Anal calcd for $\text{C}_{19}\text{H}_{20}\text{ClN}_3\text{O}_3$: C, 61.04; H, 5.39; N, 11.24; found: C, 61.05; H, 5.41; N, 11.10.
66		Yield: 72%. ^1H NMR (500 MHz, CDCl_3) δ : 11.83 (1H, s), 8.01 (1H, br t), 7.34 (2H, dd, $J = 8.6, 5.2$ Hz), 7.06 (2H, t, $J = 8.6$ Hz), 4.62 (2H, d, $J = 6.4$ Hz), 3.96 (2H, t, $J = 6.3$ Hz), 2.62-2.56 (2H, m), 2.08-1.91 (8H, m). HRMS (M+H) calcd for $\text{C}_{19}\text{H}_{21}\text{FN}_3\text{O}_3$: 358.1567; found: 358.1551. Anal calcd for $\text{C}_{19}\text{H}_{20}\text{FN}_3\text{O}_3$: C, 63.85; H, 5.64; N, 11.75; found: C, 63.72; H, 5.52; N, 11.63.

Ex.	Structure	Data
67		Yield: 80%. ^1H NMR (500 MHz, CDCl_3) δ : 11.78 (1H, s), 8.06 (1H, br t), 7.36-7.31 (1H, m), 7.14 (1H, d, $J = 7.9$ Hz), 7.06 (1H, d, $J = 9.5$ Hz), 7.00 (1H, td, $J = 8.4, 2.4$ Hz), 4.66 (2H, d, $J = 6.4$ Hz), 3.97 (2H, t, $J = 6.4$ Hz), 2.64-2.58 (2H, m), 2.09-1.91 (8H, m). HRMS ($\text{M}+\text{H}$) calcd for $\text{C}_{19}\text{H}_{21}\text{FN}_3\text{O}_3$: 358.1567; found: 358.1553. Anal calcd for $\text{C}_{19}\text{H}_{20}\text{FN}_3\text{O}_3$: C, 63.85; H, 5.64; N, 11.75; found: C, 63.86; H, 5.64; N, 11.50.
68		Yield: 75%. ^1H NMR (500 MHz, CDCl_3) δ : 11.78 (1H, s), 8.14 (1H, br t), 7.40 (1H, td, $J = 7.5, 1.2$ Hz), 7.32-7.28 (1H, m), 7.14 (1H, td, $J = 7.5, 1.0$ Hz), 7.09 (1H, dd, $J = 10.1, 8.2$ Hz), 4.70 (2H, d, $J = 6.4$ Hz), 3.95 (2H, t, $J = 6.4$ Hz), 2.65-2.59 (2H, m), 2.09-1.90 (8H, m). HRMS ($\text{M}+\text{H}$) calcd for $\text{C}_{19}\text{H}_{21}\text{FN}_3\text{O}_3$: 358.1567; found: 358.1569. Anal calcd for $\text{C}_{19}\text{H}_{20}\text{FN}_3\text{O}_3$: C, 63.85; H, 5.64; N, 11.75; found: C, 63.75; H, 5.55; N, 11.70.
69		Yield: 71%. ^1H NMR (500 MHz, CDCl_3) δ : 11.95 (1H, s), 7.99 (1H, br t), 7.14 (1H, d, $J = 7.6$ Hz), 7.13 (1H, s), 7.09 (1H, d, $J = 7.6$ Hz), 4.59 (2H, d, $J = 6.4$ Hz), 3.96 (2H, t, $J = 6.4$ Hz), 2.62-2.57 (2H, m), 2.27 (3H, s), 2.26 (3H, s), 2.07-1.90 (8H, m). HRMS ($\text{M}+\text{H}$) calcd for $\text{C}_{21}\text{H}_{26}\text{N}_3\text{O}_3$: 368.1974; found: 368.1960. Anal calcd for $\text{C}_{21}\text{H}_{25}\text{N}_3\text{O}_3$: C, 68.64; H, 6.85; N, 11.43; found: C, 67.93; H, 5.93; N, 11.27.
70		Yield: 91%. ^1H NMR (500 MHz, CDCl_3) δ : 11.70 (1H, s), 8.05 (1H, t, $J = 5.5$ Hz), 7.44 (1H, s), 7.43 (1H, d, $J = 5.5$ Hz), 7.21 (1H, dd, $J = 8.1, 1.7$ Hz), 4.61 (2H, d, $J = 6.4$ Hz), 3.97 (2H, t, $J = 6.4$ Hz), 2.64-2.58 (2H, m), 2.09-1.91 (8H, m). HRMS ($\text{M}+\text{H}$) calcd for $\text{C}_{19}\text{H}_{20}\text{Cl}_2\text{N}_3\text{O}_3$: 408.0882; found: 408.0871. Anal calcd for $\text{C}_{19}\text{H}_{19}\text{Cl}_2\text{N}_3\text{O}_3$: C, 55.89; H, 4.69; N, 10.29; found: C, 55.65; H, 4.51; N, 10.26.

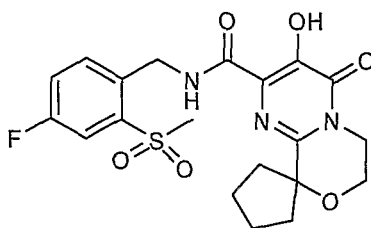
Ex.	Structure	Data
71		Yield: 81%. ^1H NMR (500 MHz, CDCl_3) δ : 11.99 (1H, s), 8.35 (1H, t, $J = 5.5$ Hz), 7.23 (1H, d, $J = 8.2$ Hz), 6.49 (1H, d, $J = 2.1$ Hz), 6.46 (1H, dd, $J = 8.2, 2.1$ Hz), 4.55 (2H, d, $J = 6.4$ Hz), 3.94 (2H, t, $J = 6.4$ Hz), 3.88 (3H, s), 3.80 (3H, s), 2.65-2.59 (2H, m), 2.10-1.89 (8H, m). HRMS ($\text{M}+\text{H}$) calcd for $\text{C}_{21}\text{H}_{26}\text{N}_3\text{O}_5$: 400.1872; found: 400.1884. Anal calcd for $\text{C}_{21}\text{H}_{25}\text{N}_3\text{O}_5$: C, 63.14; H, 6.30; N, 10.52; found: C, 62.99; H, 6.46; N, 10.49.
72		Yield: 74%. ^1H NMR (500 MHz, CDCl_3) δ : 11.86 (1H, s), 7.99 (1H, t, $J = 4.9$ Hz), 7.17 (1H, d, $J = 7.0$ Hz), 7.15-7.12 (1H, m), 6.99 (1H, t, $J = 8.9$ Hz), 4.58 (2H, d, $J = 6.4$ Hz), 3.96 (2H, t, $J = 6.4$ Hz), 2.63-2.57 (2H, m), 2.28 (3H, d, $J = 1.5$ Hz), 2.08-1.91 (8H, m). HRMS ($\text{M}+\text{H}$) calcd for $\text{C}_{20}\text{H}_{23}\text{FN}_3\text{O}_3$: 372.1723; found: 372.1737. Anal calcd for $\text{C}_{20}\text{H}_{22}\text{FN}_3\text{O}_3$: C, 64.67; H, 5.97; N, 11.31; found: C, 64.73; H, 6.20; N, 11.30.
73		Yield: 73%. ^1H NMR (500 MHz, CDCl_3) δ : 11.82 (1H, s), 8.02 (1H, br t), 7.17 (1H, t, $J = 7.8$ Hz), 7.02 (1H, d, $J = 8.6$ Hz), 7.00 (1H, d, $J = 10.7$ Hz), 4.61 (2H, d, $J = 6.1$ Hz), 3.96 (2H, t, $J = 6.4$ Hz), 2.63-2.57 (2H, m), 2.26 (3H, s), 2.08-1.91 (8H, m). HRMS ($\text{M}+\text{H}$) calcd for $\text{C}_{20}\text{H}_{23}\text{FN}_3\text{O}_3$: 372.1723; found: 372.1714. Anal calcd for $\text{C}_{20}\text{H}_{22}\text{FN}_3\text{O}_3$: C, 64.67; H, 5.97; N, 11.31; found: C, 64.56; H, 6.08; N, 11.41.
74		Yield: 73%. ^1H NMR (500 MHz, CDCl_3) δ : 11.78 (1H, s), 7.91 (1H, d, $J = 7.6$ Hz), 7.36-7.33 (2H, m), 7.06 (2H, td, $J = 8.6, 1.2$ Hz), 5.25-5.19 (H, m), 3.96 (2H, t, $J = 6.4$ Hz), 2.64-2.56 (2H, m), 2.11-1.91 (8H, m), 1.62 (3H, d, $J = 7.0$ Hz). HRMS ($\text{M}+\text{H}$) calcd for $\text{C}_{20}\text{H}_{23}\text{FN}_3\text{O}_3$: 372.1723; found: 372.1708. Anal calcd for $\text{C}_{20}\text{H}_{22}\text{FN}_3\text{O}_3$: C, 64.67; H, 5.97; N, 11.31; found: C, 63.20; H, 6.22; N, 10.74.
75		Yield: 79%. ^1H NMR (500 MHz, CDCl_3) δ : 11.67 (1H, s), 8.13 (1H, br t), 7.11-7.03 (2H, m), 6.99-6.94 (1H, m), 4.68 (2H, d, $J = 6.4$ Hz), 3.96 (2H, t, $J = 6.4$ Hz), 2.65-2.59 (2H, m), 2.10-1.91 (8H, m). HRMS ($\text{M}+\text{H}$) calcd for $\text{C}_{19}\text{H}_{20}\text{F}_2\text{N}_3\text{O}_3$: 376.1473; found: 376.1483. Anal calcd for $\text{C}_{19}\text{H}_{19}\text{F}_2\text{N}_3\text{O}_3$: C, 60.79; H, 5.10; N, 11.19; found: C, 60.60; H, 5.21; N, 11.17.

Ex.	Structure	Data
76		Yield: 75%. ^1H NMR (500 MHz, CDCl_3) δ : 11.62 (1H, s), 8.30 (1H, t, $J = 5.8$ Hz), 7.41 (1H, d, $J = 2.5$ Hz), 7.34 (1H, d, $J = 8.6$ Hz), 7.25 (1H, dd, $J = 8.2, 2.4$ Hz), 4.69 (2H, d, $J = 6.7$ Hz), 3.96 (2H, t, $J = 6.3$ Hz), 2.66-2.60 (2H, m), 2.11-1.91 (8H, m). HRMS ($\text{M}+\text{H}$) calcd for $\text{C}_{19}\text{H}_{20}\text{Cl}_2\text{N}_3\text{O}_3$: 408.0882; found: 408.0879. Anal calcd for $\text{C}_{19}\text{H}_{19}\text{Cl}_2\text{N}_3\text{O}_3$: C, 55.89; H, 4.69; N, 10.29; found: C, 55.66; H, 4.83; N, 10.27.
77		Yield: 51%. ^1H NMR (500 MHz, CDCl_3) δ : 11.74 (1H, s), 8.97 (1H, t, $J = 6.4$ Hz), 8.41 (1H, s), 8.16 (1H, s), 7.44 (1H, dd, $J = 8.5, 2.8$ Hz), 7.35 (1H, dd, $J = 8.5, 4.9$ Hz), 7.15 (1H, td, $J = 8.5, 2.8$ Hz), 4.46 (2H, d, $J = 6.7$ Hz), 3.94 (2H, t, $J = 6.4$ Hz), 2.75-2.69 (2H, m), 2.16-1.90 (8H, m). HRMS ($\text{M}+\text{H}$) calcd for $\text{C}_{21}\text{H}_{22}\text{FN}_6\text{O}_3$: 425.1737; found: 425.1735. Anal calcd for $\text{C}_{21}\text{H}_{21}\text{FN}_6\text{O}_3$: C, 59.42; H, 4.98; N, 19.80; found: C, 59.20; H, 4.88; N, 19.51.
78		Yield: 59%. ^1H NMR (500 MHz, CDCl_3) δ : 11.81 (1H, s), 9.07 (1H, t, $J = 6.4$ Hz), 8.46 (1H, s), 8.18 (1H, s), 7.73 (1H, dd, $J = 8.4, 6.0$ Hz), 7.22 (1H, td, $J = 8.2, 2.4$ Hz), 7.12 (1H, dd, $J = 8.6, 2.4$ Hz), 4.48 (2H, d, $J = 6.7$ Hz), 3.94 (2H, t, $J = 6.4$ Hz), 2.75-2.69 (2H, m), 2.17-1.89 (8H, m). HRMS ($\text{M}+\text{H}$) calcd for $\text{C}_{21}\text{H}_{22}\text{FN}_6\text{O}_3$: 425.1737; found: 425.1727. Anal calcd for $\text{C}_{21}\text{H}_{21}\text{FN}_6\text{O}_3$: C, 59.42; H, 4.98; N, 19.80; found: C, 59.35; H, 4.69; N, 19.85.
79		Yield: 53%. ^1H NMR (500 MHz, CDCl_3) δ : 11.96 (1H, s), 8.42 (1H, br t), 7.49 (1H, dd, $J = 8.5, 6.4$ Hz), 7.18 (1H, dd, $J = 9.2, 2.4$ Hz), 7.08 (1H, td, $J = 8.2, 2.4$ Hz), 4.99 (1H, dd, $J = 14.4, 8.5$ Hz), 4.42 (1H, dd, $J = 14.4, 3.7$ Hz), 3.99-3.83 (3H, m), 3.45 (1H, dt, $J = 12.5, 4.0$ Hz), 3.28-3.25 (2H, m), 2.70-2.61 (2H, m), 2.45-2.31 (2H, m), 2.03-1.9 (10H, m). HRMS ($\text{M}+\text{H}$) calcd for $\text{C}_{23}\text{H}_{28}\text{FN}_4\text{O}_5\text{S}$: 491.1764; found: 491.1776. Anal calcd for $\text{C}_{23}\text{H}_{27}\text{FN}_4\text{O}_5\text{S}$: C, 56.31; H, 5.54; N, 11.41; found: C, 56.07; H, 5.60; N, 11.25.

Ex.	Structure	Data
80		Yield: 66%. ¹ H NMR (500 MHz, CDCl ₃) δ: 11.87 (1H, s), 9.11 (1H, t, J = 6.4 Hz), 8.45 (1H, s), 8.17 (1H, s), 7.73 (1H, dd, J = 7.3, 1.2 Hz), 7.51 (1H, td, J = 7.3, 1.2 Hz), 7.47 (1H, td, J = 7.6, 1.5 Hz), 7.36 (1H, dd, J = 7.6, 1.0 Hz), 4.51 (2H, d, J = 6.7 Hz), 3.94 (2H, t, J = 6.4 Hz), 2.76-2.70 (2H, m), 2.17-1.89 (8H, m). HRMS (M+H) calcd for C ₂₁ H ₂₃ N ₆ O ₃ : 407.1832; found: 407.1833. Anal calcd for C ₂₁ H ₂₂ N ₆ O ₃ : C, 62.05; H, 5.45; N, 20.67; found: C, 61.86; H, 5.48; N, 20.90.
81		Yield: 57%. ¹ H NMR (500 MHz, CDCl ₃) δ: 11.60 (1H, s), 8.78 (1H, t, J = 6.4 Hz), 7.76 (1H, dd, J = 8.2, 2.4 Hz), 7.73 (1H, dd, J = 8.6, 5.2 Hz), 7.35 (1H, td, J = 8.2, 2.8 Hz), 4.86 (2H, d, J = 7.0 Hz), 3.93 (2H, t, J = 6.4 Hz), 3.19 (3H, s), 2.68-2.62 (2H, m), 2.15-1.88 (8H, m). HRMS (M+H) calcd for C ₂₀ H ₂₃ FN ₃ O ₅ S: 436.1342; found: 436.1325. Anal calcd for C ₂₀ H ₂₂ FN ₃ O ₅ S: C, 55.16; H, 5.09; N, 9.65; found: C, 55.00; H, 4.93; N, 9.45.
82		Yield: 64%. ¹ H NMR (500 MHz, CDCl ₃) δ: 11.48 (1H, br s), 8.82 (1H, t, J = 6.4 Hz), 7.71 (1H, dd, J = 8.2, 5.5 Hz), 7.51 (1H, dd, J = 8.2, 2.1 Hz), 7.29 (1H, dd, J = 8.2, 2.4 Hz), 4.85 (2H, d, J = 7.0 Hz), 3.94 (2H, t, J = 6.4 Hz), 2.91 (6H, s), 2.69-2.64 (2H, m), 2.15-1.89 (8H, m). HRMS (M+H) calcd for C ₂₁ H ₂₆ FN ₄ O ₅ S: 465.1608; found: 465.1593. Anal calcd for C ₂₁ H ₂₅ FN ₄ O ₅ S•0.44 CF ₃ CO ₂ H: C, 51.06; H, 4.98; N, 10.89; found: C, 51.41; H, 5.18; N, 10.50.
83		Yield: 48%. ¹ H NMR (500 MHz, CDCl ₃) δ: 12.01 (1H, s), 8.43-8.41 (1H, m), 7.50-7.48 (1H, m), 7.46-7.45 (1H, m), 7.35-7.35 (2H, m), 5.02 (1H, dd, J = 14.3, 8.6 Hz), 4.49 (1H, dd, J = 14.3, 4.0 Hz), 3.96-3.87 (3H, m), 3.46-3.42 (1H, m), 3.27-3.24 (2H, m), 2.71-2.61 (2H, m), 2.45-2.31 (2H, m), 2.02-1.84 (10H, m). HRMS (M+H) calcd for C ₂₃ H ₂₉ N ₄ O ₅ S: 473.1859; found: 473.1866. Anal calcd for C ₂₃ H ₂₈ N ₄ O ₅ S•0.12 C ₂ H ₅ OH•0.3 H ₂ O: C, 57.73; H, 6.11; N, 11.59; found: C, 57.48; H, 5.67; N, 11.47.

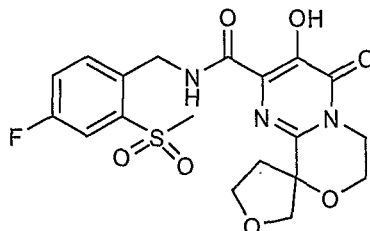
Ex.	Structure	Data
84		Yield = 47%. ^1H NMR (300 MHz, CDCl_3) δ : 1.65-2.02 (8 H, m), 2.07 (2 H, t, $J = 7$ Hz), 4.03 (2 H, t, $J = 7$ Hz), 4.55 (2 H, d, $J = 6.2$ Hz), 7.02 (2 H, t, $J = 8.6$ Hz), 7.29 (2 H, dd, $J = 8.6, 5.3$ Hz), 7.90 (1 H, brs), 12.09 (1 H, s). HRMS (M+H) calcd for $\text{C}_{19}\text{H}_{21}\text{FN}_3\text{O}_3$: 358.1567; found: 358.1578.
85		Yield = 54%. ^1H NMR (300 MHz, CDCl_3) δ : 1.64 1.78 (4 H, m), 1.87-2.01 (4 H, m), 2.07 (2 H, t, $J = 7$ Hz), 3.15 (3H, s), 4.01 (2 H, t, $J = 7$ Hz), 4.82 (2 H, d, $J = 7.0$ Hz), 7.32 (1 H, dd, $J = 7.9, 2.7$ Hz), 7.62-7.78 (2 H, m), 8.55 (1 H, t, $J = 7.0$ Hz), 11.87 (1 H, s). HRMS (M+H) calcd for $\text{C}_{20}\text{H}_{23}\text{FN}_3\text{O}_5\text{S}$: 436.1342; found 436.1341.
86		Yield = 15%. ^1H NMR (300 MHz, CDCl_3) δ : 1.62-1.79 (4 H, m), 1.86-2.02 (4 H, m), 2.07 (2 H, t, $J = 7$ Hz), 2.86 (6 H, s), 4.00 (2H, t, $J = 7$ Hz), 4.80 (2 H, d, $J = 6.6$ Hz), 7.19-7.30 (1 H, m), 7.50 (1 H, dd, $J = 8.4, 2.6$ Hz), 7.66 (1 H, dd, $J = 8.6, 5.3$ Hz), 8.54 (1 H, t, $J = 6.8$ Hz), 12.00 (1 H, s). HRMS (M+H) calcd for $\text{C}_{21}\text{H}_{26}\text{FN}_4\text{O}_5\text{S}$: 465.1608; found 465.1626.
87		Yield = 13%. ^1H NMR (300 MHz, CDCl_3) δ : 1.64-1.83 (4 H, m), 1.87-2.05 (4 H, m), 1.87-2.05 (4 H, m), 2.09 (2 H, t, $J = 7$ Hz), 4.01 (2 H, t, $J = 7$ Hz), 4.44 (2 H, d, $J = 6.6$ Hz), 7.08 (1H, dd, $J = 8.4, 2.5$ Hz), 7.19(1 H, dt, $J = 8.4, 2.5$ Hz), 7.67 (1 H, dd, $J = 8.4, 5.9$ Hz), 8.15 (1 H, s), 8.42 (1 H, s), 8.77 (1 H, t, $J = 6.8$ Hz), 12.02 (1 H, s). HRMS (M+H) calcd for $\text{C}_{21}\text{H}_{22}\text{FN}_6\text{O}_3$: 425.1737; found 425.1741.
88		Yield: 27%. ^1H -NMR (300 MHz, $\text{CDCl}_3/\text{MeOD}$) δ : 7.31-7.27 (2H, m), 7.00 (2H, t, $J = 8.6$ Hz), 4.53 (2H, s), 3.98 (4H, s), 2.98-2.84 (4H, m), 2.14 (2H, td, $J = 10.3, 5.4$ Hz), 1.84 (2H, dd, $J = 12.8, 1.1$ Hz). HRMS (M+H) calcd for $\text{C}_{19}\text{H}_{22}\text{N}_4\text{O}_4\text{F}$: 389.1625; found: 389.1610.

Example 89



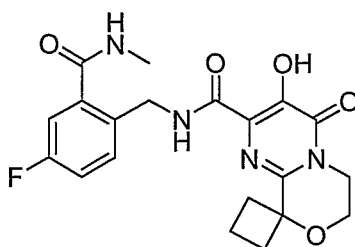
A mixture of example **18** (52 mg, 0.124 mmol) and mCPBA (64.2 mg, 0.372 mmol) in CH₂Cl₂ was stirred at room temperature for 4 h. Then, concentrated and purified by preparative HPLC to afford example **89** (26.2 mg, 47%) as a purple solid. ¹H NMR (500 MHz, CDCl₃) δ: 11.69 (1H, s), 8.54 (1H, t, J = 6.4 Hz), 7.75 (1H, dd, J = 8.2, 2.7 Hz), 7.70 (1H, dd, J = 8.6, 5.2 Hz), 7.34 (1H, td, J = 7.9, 2.5 Hz), 4.81 (2H, d, J = 6.7 Hz), 3.99-3.94 (4H, m), 3.16 (3H, s), 2.21-2.16 (2H, m), 2.06-2.00 (2H, m), 1.94-1.82 (4H, m). HRMS (M+H) calcd for C₂₀H₂₃FN₃O₆S: 452.1292; found: 452.1286.

Example 90



Example **90** was prepared according to the procedure for example **89** using example **39** to afford product in 38% as a purple solid. ¹H NMR (500 MHz, CDCl₃) δ: 11.82 (1H, bs), 8.57 (1H, t, J = 5.8 Hz), 7.75 (1H, dd, J = 8.0, 2.6 Hz), 7.69 (1H, dd, J = 8.4, 5.0 Hz), 7.33 (1H, td, J = 7.9, 2.4 Hz), 4.87-4.74 (2H, m), 4.20-3.98 (8H, m), 3.18 (3H, s), 2.61-2.56 (1H, m), 2.34-2.29 (1H, m). HRMS (M+H) calcd for C₁₉H₂₁FN₃O₇S: 454.1084; found: 454.1096.

Example 91

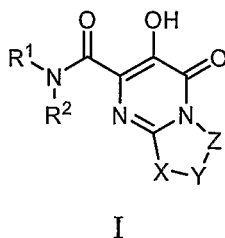


A solution of intermediate **45** (0.096 g, 0.190 mmol) in dichloromethane (5
5 mL) and trifluoroacetic acid (5 mL) was stirred for 2 hours, and then solvent was
removed in-vacuo to give a yellow oil. The oil was triturated with a minimal volume
of 95% ethanol, and solids were collected by filtration to give **91** (0.056 g, 71%) as a
white solid after vacuum pump drying: ¹H NMR (500 MHz, DMSO-D₆) δ: 12.19
(1H, s), 9.37 (1H, t, *J* = 6.4 Hz), 8.56 - 8.61 (1H, m), 7.44 (1H, dd, *J* = 8.5, 5.8 Hz),
10 7.36 (1H, dd, *J* = 9.3, 2.6 Hz), 7.31 (1H, td, *J* = 8.5, 2.6 Hz), 4.58 (2H, d, *J* = 6.7 Hz),
3.92 (2H, t, *J* = 5.3 Hz), 3.80 (2H, t, *J* = 5.2 Hz), 2.79 (3H, d, *J* = 4.6 Hz), 2.65-2.72
(2H, m), 2.19-2.25 (2H, m), 2.12 - 2.18 (1H, m), 1.88-1.96 (1H, m). ¹³C NMR (126
MHz, DMSO-D₆) δ: 167.68, 161.68, 159.73, 156.73, 150.37, 145.81, 137.24, 137.19,
132.61, 131.33, 131.27, 125.22, 116.87, 116.70, 114.88, 114.70, 77.99, 57.88, 41.96,
15 40.33, 33.95, 26.06, 13.08. HRMS (M+H) calc'd for C₂₀H₂₂N₄O₅F: 417.1574; found:
417.1589.

CLAIMS

I claim:

- 5 1. A compound of Formula I



10 wherein:

R^1 is $C_{1-6}(Ar^1)alkyl$;

R^2 is hydrogen, $C_{1-6}alkyl$, or OR^6 ;

15

R^3 is hydrogen, halo, hydroxy, cyano, $C_{1-6}alkyl$, $C_{3-7}cycloalkyl$, $C_{1-6}haloalkyl$, $C_{1-6}alkoxy$, $C_{1-6}alkylthio$, $C_{1-6}haloalkoxy$, $CON(R^6)(R^6)$, SOR^7 , SO_2R^7 , $SO_2N(R^6)(R^6)$, or Ar^2 ;

20 R^4 is hydrogen, halo, hydroxy, cyano, $C_{1-6}alkyl$, $C_{1-6}alkoxy$, $C_{1-6}haloalkyl$, or $C_{1-6}haloalkoxy$;

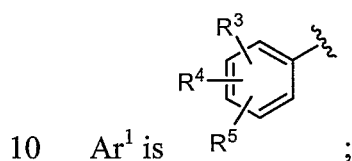
R^5 is hydrogen, halo, hydroxy, cyano, $C_{1-6}alkyl$, $C_{1-6}alkoxy$, $C_{1-6}haloalkyl$, or $C_{1-6}haloalkoxy$;

25

R^6 is hydrogen or $C_{1-6}alkyl$;

R^7 is $C_{1-6}alkyl$;

- R^8 and R^9 taken together are CH_2CH_2 , $CH_2CH_2CH_2$, $CH_2CH_2CH_2CH_2$, $CH_2CH_2CH_2CH_2CH_2$, $CH_2CH_2CH_2CH_2CH_2CH_2$, OCH_2CH_2 , CH_2OCH_2 , $OCH_2CH_2CH_2$, $CH_2OCH_2CH_2$, $OCH_2CH_2CH_2CH_2$, $CH_2OCH_2CH_2CH_2$, $CH_2CH_2OCH_2CH_2$, $OCH_2CH_2CH_2CH_2CH_2$, $CH_2OCH_2CH_2CH_2CH_2$, $CH_2CH_2OCH_2CH_2CH_2$, $N(R^6)CH_2CH_2$, $CH_2N(R^6)CH_2$, $N(R^6)CH_2CH_2CH_2$, $CH_2N(R^6)CH_2CH_2$, $N(R^6)CH_2CH_2CH_2CH_2$, $CH_2N(R^6)CH_2CH_2CH_2$, $CH_2CH_2N(R^6)CH_2CH_2$, $N(R^6)CH_2CH_2CH_2CH_2CH_2$, $CH_2N(R^6)CH_2CH_2CH_2CH_2$, or $CH_2CH_2N(R^6)CH_2CH_2CH_2$;



Ar^2 is tetrazolyl, triazolyl, imidazolyl, pyrazolyl, pyrrolyl, or dioxothiazinyl, and is substituted with 0-2 substituents selected from the group consisting of amino, oxo, halo, cyano, and C_{1-6} alkyl; and

15

X-Y-Z is $C(R^8)(R^9)CH_2CH_2$, $C(R^8)(R^9)CH_2CH_2CH_2$, $C(R^8)(R^9)CH_2CH_2CH_2CH_2$, $C(R^8)(R^9)OCH_2$, $C(R^8)(R^9)OCH_2CH_2$, or $C(R^8)(R^9)OCH_2CH_2CH_2$;

or a pharmaceutically acceptable salt or solvate thereof.

20

2. A compound of claim 1 where X-Y-Z is $C(R^8)(R^9)CH_2CH_2$, $C(R^8)(R^9)CH_2CH_2CH_2$, or $C(R^8)(R^9)CH_2CH_2CH_2CH_2$.

3. A compound of claim 2 where R^8 and R^9 taken together are $CH_2CH_2CH_2$, $CH_2CH_2CH_2CH_2$, $CH_2CH_2CH_2CH_2CH_2$, $CH_2OCH_2CH_2$, $CH_2CH_2OCH_2CH_2$, $CH_2N(R^6)CH_2CH_2$, or $CH_2CH_2N(R^6)CH_2CH_2$.

4. A compound of claim 2 selected from the group consisting of

N-[(4-fluorophenyl)methyl]-7',8'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclopentane-1,9'(6'H)-[4H]pyrido[1,2-a]pyrimidine]-2'-carboxamide;

5 N-[(4-fluoro-3-methylphenyl)methyl]-7',8'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclopentane-1,9'(6'H)-[4H]pyrido[1,2-a]pyrimidine]-2'-carboxamide;

N-[[2-(1*H*-1,2,4-triazol-1-yl)phenyl]methyl]-7',8'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclopentane-1,9'(6'*H*)-[4*H*]pyrido[1,2-*a*]pyrimidine]-2'-carboxamide;

10 N-[[4-fluoro-2-(1*H*-1,2,4-triazol-1-yl)phenyl]methyl]-7',8'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclopentane-1,9'(6'*H*)-[4*H*]pyrido[1,2-*a*]pyrimidine]-2'-carboxamide;

15 N-[[5-fluoro-2-(1*H*-1,2,4-triazol-1-yl)phenyl]methyl]-7',8'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclopentane-1,9'(6'*H*)-[4*H*]pyrido[1,2-*a*]pyrimidine]-2'-carboxamide;

20 N-[[4-fluoro-2-(2*H*-1,2,3-triazol-2-yl)phenyl]methyl]-7',8'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclopentane-1,9'(6'*H*)-[4*H*]pyrido[1,2-*a*]pyrimidine]-2'-carboxamide;

N-[[4-fluoro-2-(1*H*-imidazol-1-yl)phenyl]methyl]-7',8'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclopentane-1,9'(6'*H*)-[4*H*]pyrido[1,2-*a*]pyrimidine]-2'-carboxamide;

25 N-[[2-(tetrahydro-1,1-dioxido-2*H*-1,2-thiazin-2-yl)phenyl]methyl]-7',8'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclopentane-1,9'(6'*H*)-[4*H*]pyrido[1,2-*a*]pyrimidine]-2'-carboxamide;

30 N-[[4-fluoro-2-(tetrahydro-1,1-dioxido-2*H*-1,2-thiazin-2-yl)phenyl]methyl]-7',8'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclopentane-1,9'(6'*H*)-[4*H*]pyrido[1,2-*a*]pyrimidine]-2'-carboxamide;

N-[[2-[(dimethylamino)sulfonyl]-4-fluorophenyl]methyl]-7',8'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclopentane-1,9'(6'*H*)-[4*H*]pyrido[1,2-*a*]pyrimidine]-2'-carboxamide;

- 5 *N*-[[4-fluoro-2-(methylsulfonyl)phenyl]methyl]-7',8'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclopentane-1,9'(6'*H*)-[4*H*]pyrido[1,2-*a*]pyrimidine]-2'-carboxamide;

- 10 *N*-[[3-fluoro-2-(1*H*-1,2,4-triazol-1-yl)phenyl]methyl]-7',8'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclopentane-1,9'(6'*H*)-[4*H*]pyrido[1,2-*a*]pyrimidine]-2'-carboxamide;

N-(phenylmethyl)-7',8'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclobutane-1,9'(6'*H*)-[4*H*]pyrido[1,2-*a*]pyrimidine]-2'-carboxamide;

- 15 *N*-[(4-fluorophenyl)methyl]-4,5,6',7'-tetrahydro-3'-hydroxy-4'-oxo-spiro[furan-3(2*H*),9'(4'*H*)-pyrimido[2,1-*c*][1,4]oxazine]-2'-carboxamide;

- 20 *N*-[(4-fluoro-3-methylphenyl)methyl]-4,5,6',7'-tetrahydro-3'-hydroxy-4'-oxo-spiro[furan-3(2*H*),9'(4'*H*)-pyrimido[2,1-*c*][1,4]oxazine]-2'-carboxamide;

N-[[4-fluoro-2-(1*H*-1,2,4-triazol-1-yl)phenyl]methyl]-4,5,6',7'-tetrahydro-3'-hydroxy-4'-oxo-spiro[furan-3(2*H*),9'(4'*H*)-pyrimido[2,1-*c*][1,4]oxazine]-2'-carboxamide;

- 25 *N*-[[4-fluoro-2-(methylthio)phenyl]methyl]-4,5,6',7'-tetrahydro-3'-hydroxy-4'-oxo-spiro[furan-3(2*H*),9'(4'*H*)-pyrimido[2,1-*c*][1,4]oxazine]-2'-carboxamide;

- 30 *N*-[(4-fluorophenyl)methyl]-2,3,5,6,6',7'-hexahydro-3'-hydroxy-4'-oxo-spiro[4*H*-pyran-4,9'(4'*H*)-pyrimido[2,1-*c*][1,4]oxazine]-2'-carboxamide;

N-[[4-fluoro-2-(1*H*-1,2,4-triazol-1-yl)phenyl]methyl]-2,3,5,6,6',7'-hexahydro-3'-hydroxy-4'-oxo-spiro[4*H*-pyran-4,9'(4'*H*)-pyrimido[2,1-*c*][1,4]oxazine]-2'-carboxamide;

N-[[4-fluoro-2-(tetrahydro-1,1-dioxido-2*H*-1,2-thiazin-2-yl)phenyl]methyl]-2,3,5,6,6',7'-hexahydro-3'-hydroxy-4'-oxo-spiro[4*H*-pyran-4,9'(4'*H*)-pyrimido[2,1-*c*][1,4]oxazine]-2'-carboxamide;

5 *N*-[[2-(tetrahydro-1,1-dioxido-2*H*-1,2-thiazin-2-yl)phenyl]methyl]-2,3,5,6,6',7'-hexahydro-3'-hydroxy-4'-oxo-spiro[4*H*-pyran-4,9'(4'*H*)-pyrimido[2,1-*c*][1,4]oxazine]-2'-carboxamide;

10 *N*-[[4-fluoro-2-(methylsulfonyl)phenyl]methyl]-2,3,5,6,6',7'-hexahydro-3'-hydroxy-4'-oxo-spiro[4*H*-pyran-4,9'(4'*H*)-pyrimido[2,1-*c*][1,4]oxazine]-2'-carboxamide;

15 *N*-[(4-fluoro-3-methylphenyl)methyl]-2,3,5,6,6',7'-hexahydro-3'-hydroxy-4'-oxo-spiro[4*H*-pyran-4,9'(4'*H*)-pyrimido[2,1-*c*][1,4]oxazine]-2'-carboxamide;

N-[(2,4-dimethoxyphenyl)methyl]-2,3,5,6,6',7'-hexahydro-3'-hydroxy-4'-oxo-spiro[4*H*-pyran-4,9'(4'*H*)-pyrimido[2,1-*c*][1,4]oxazine]-2'-carboxamide;

20 *N*-[[2-[(dimethylamino)sulfonyl]-4-fluorophenyl]methyl]-2,3,5,6,6',7'-hexahydro-3'-hydroxy-4'-oxo-spiro[4*H*-pyran-4,9'(4'*H*)-pyrimido[2,1-*c*][1,4]oxazine]-2'-carboxamide

25 *N*-[(3,4-dimethylphenyl)methyl]-2,3,5,6,6',7'-hexahydro-3'-hydroxy-4'-oxo-spiro[4*H*-pyran-4,9'(4'*H*)-pyrimido[2,1-*c*][1,4]oxazine]-2'-carboxamide;

N-[[4-fluoro-2-(5-methyl-1*H*-1,2,4-triazol-1-yl)phenyl]methyl]-2,3,5,6,6',7'-hexahydro-3'-hydroxy-4'-oxo-spiro[4*H*-pyran-4,9'(4'*H*)-pyrimido[2,1-*c*][1,4]oxazine]-2'-carboxamide;

30 *N*-[[4-fluoro-2-(3-methyl-1*H*-1,2,4-triazol-1-yl)phenyl]methyl]-2,3,5,6,6',7'-hexahydro-3'-hydroxy-4'-oxo-spiro[4*H*-pyran-4,9'(4'*H*)-pyrimido[2,1-*c*][1,4]oxazine]-2'-carboxamide;

N-[[4-fluoro-2-(1H-1,2,4-triazol-1-yl)phenyl]methyl]-6',7'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclobutane-1,9'(4'H)-pyrimido[2,1-c][1,4]oxazine]-2'-carboxamide;

5 N-[(4-fluorophenyl)methyl]-6',7'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclobutane-1,9'(4'H)-pyrimido[2,1-c][1,4]oxazine]-2'-carboxamide;

N-[[4-fluoro-2-(methylsulfonyl)phenyl]methyl]-6',7'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclobutane-1,9'(4'H)-pyrimido[2,1-c][1,4]oxazine]-2'-carboxamide;

10

N-[[2-[(dimethylamino)sulfonyl]-4-fluorophenyl]methyl]-6',7'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclobutane-1,9'(4'H)-pyrimido[2,1-c][1,4]oxazine]-2'-carboxamide;

15 N-[[4-fluoro-2-(tetrahydro-1,1-dioxido-2H-1,2-thiazin-2-yl)phenyl]methyl]-6',7'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclobutane-1,9'(4'H)-pyrimido[2,1-c][1,4]oxazine]-2'-carboxamide;

20 N-[[2-(tetrahydro-1,1-dioxido-2H-1,2-thiazin-2-yl)phenyl]methyl]-6',7'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclobutane-1,9'(4'H)-pyrimido[2,1-c][1,4]oxazine]-2'-carboxamide;

25 N-[[4-fluoro-2-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl]methyl]-6',7'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclobutane-1,9'(4'H)-pyrimido[2,1-c][1,4]oxazine]-2'-carboxamide;

N-[[4-fluoro-2-(methylsulfonyl)phenyl]methyl]-7',8'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclobutane-1,10'(4'H)-[6H]pyrimido[2,1-c][1,4]oxazepine]-2'-carboxamide;

30

N-[(4-fluorophenyl)methyl]-7',8'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclobutane-1,10'(4'H)-[6H]pyrimido[2,1-c][1,4]oxazepine]-2'-carboxamide;

N-[[4-fluoro-2-(1*H*-1,2,4-triazol-1-yl)phenyl]methyl]-7',8'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclobutane-1,10'(4'*H*)-[6*H*]pyrimido[2,1-*c*][1,4]oxazepine]-2'-carboxamide; and

- 5 *N*-[[2-[(dimethylamino)sulfonyl]-4-fluorophenyl]methyl]-7',8'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclobutane-1,10'(4'*H*)-[6*H*]pyrimido[2,1-*c*][1,4]oxazepine]-2'-carboxamide;

or a pharmaceutically acceptable salt or solvate thereof.

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5. A compound of claim 1 where X-Y-Z is C(R⁸)(R⁹)OCH₂,
C(R⁸)(R⁹)OCH₂CH₂, or C(R⁸)(R⁹)OCH₂CH₂CH₂.
6. A compound of claim 5 where R⁸ and R⁹ taken together are CH₂CH₂CH₂,
15 CH₂CH₂CH₂CH₂, CH₂CH₂CH₂CH₂CH₂, CH₂CH₂CH₂CH₂CH₂CH₂, CH₂OCH₂CH₂,
CH₂CH₂OCH₂CH₂, CH₂N(R⁶)CH₂CH₂, or CH₂CH₂N(R⁶)CH₂CH₂.

7. A compound of claim 5 selected from the group consisting of
- 20 *N*-[(4-methylphenyl)methyl]-7',8'-dihydro-3'-hydroxy-4'-oxo-
spiro[cyclobutane-1,9'(6'*H*)-[4*H*]pyrido[1,2-*a*]pyrimidine]-2'-carboxamide;

N-[(4-methoxyphenyl)methyl]-7',8'-dihydro-3'-hydroxy-4'-oxo-
spiro[cyclobutane-1,9'(6'*H*)-[4*H*]pyrido[1,2-*a*]pyrimidine]-2'-carboxamide;

25

N-[(4-chlorophenyl)methyl]-7',8'-dihydro-3'-hydroxy-4'-oxo-
spiro[cyclobutane-1,9'(6'*H*)-[4*H*]pyrido[1,2-*a*]pyrimidine]-2'-carboxamide;

N-[(4-fluorophenyl)methyl]-7',8'-dihydro-3'-hydroxy-4'-oxo-
30 spiro[cyclobutane-1,9'(6'*H*)-[4*H*]pyrido[1,2-*a*]pyrimidine]-2'-carboxamide;

N-[(3-fluorophenyl)methyl]-7',8'-dihydro-3'-hydroxy-4'-oxo-
spiro[cyclobutane-1,9'(6'*H*)-[4*H*]pyrido[1,2-*a*]pyrimidine]-2'-carboxamide;

N-[(2-fluorophenyl)methyl]-7',8'-dihydro-3'-hydroxy-4'-oxo-
spiro[cyclobutane-1,9'(6'*H*)-[4*H*]pyrido[1,2-*a*]pyrimidine]-2'-carboxamide;

N-[(3,4-dimethylphenyl)methyl]-7',8'-dihydro-3'-hydroxy-4'-oxo-
5 spiro[cyclobutane-1,9'(6'*H*)-[4*H*]pyrido[1,2-*a*]pyrimidine]-2'-carboxamide;

N-[(3,4-dichlorophenyl)methyl]-7',8'-dihydro-3'-hydroxy-4'-oxo-
spiro[cyclobutane-1,9'(6'*H*)-[4*H*]pyrido[1,2-*a*]pyrimidine]-2'-carboxamide;

10 *N*-[(2,4-dimethoxyphenyl)methyl]-7',8'-dihydro-3'-hydroxy-4'-oxo-
spiro[cyclobutane-1,9'(6'*H*)-[4*H*]pyrido[1,2-*a*]pyrimidine]-2'-carboxamide;

N-[(4-fluoro-3-methylphenyl)methyl]-7',8'-dihydro-3'-hydroxy-4'-oxo-
spiro[cyclobutane-1,9'(6'*H*)-[4*H*]pyrido[1,2-*a*]pyrimidine]-2'-carboxamide;
15

N-[(3-fluoro-4-methylphenyl)methyl]-7',8'-dihydro-3'-hydroxy-4'-oxo-
spiro[cyclobutane-1,9'(6'*H*)-[4*H*]pyrido[1,2-*a*]pyrimidine]-2'-carboxamide;

N-[1-(4-fluorophenyl)ethyl]-7',8'-dihydro-3'-hydroxy-4'-oxo-
20 spiro[cyclobutane-1,9'(6'*H*)-[4*H*]pyrido[1,2-*a*]pyrimidine]-2'-carboxamide;

N-[(2,5-difluorophenyl)methyl]-7',8'-dihydro-3'-hydroxy-4'-oxo-
spiro[cyclobutane-1,9'(6'*H*)-[4*H*]pyrido[1,2-*a*]pyrimidine]-2'-carboxamide;

25 *N*-[(2,5-dichlorophenyl)methyl]-7',8'-dihydro-3'-hydroxy-4'-oxo-
spiro[cyclobutane-1,9'(6'*H*)-[4*H*]pyrido[1,2-*a*]pyrimidine]-2'-carboxamide;

N-[[5-fluoro-2-(1*H*-1,2,4-triazol-1-yl)phenyl]methyl]-7',8'-dihydro-3'-
hydroxy-4'-oxo-spiro[cyclobutane-1,9'(6'*H*)-[4*H*]pyrido[1,2-*a*]pyrimidine]-2'-
30 carboxamide;

N-[[4-fluoro-2-(1*H*-1,2,4-triazol-1-yl)phenyl]methyl]-7',8'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclobutane-1,9'(6'*H*)-[4*H*]pyrido[1,2-*a*]pyrimidine]-2'-carboxamide;

5 *N*-[[4-fluoro-2-(tetrahydro-1,1-dioxido-2*H*-1,2-thiazin-2-yl)phenyl]methyl]-7',8'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclobutane-1,9'(6'*H*)-[4*H*]pyrido[1,2-*a*]pyrimidine]-2'-carboxamide;

10 *N*-[[2-(1*H*-1,2,4-triazol-1-yl)phenyl]methyl]-7',8'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclobutane-1,9'(6'*H*)-[4*H*]pyrido[1,2-*a*]pyrimidine]-2'-carboxamide;

N-[[4-fluoro-2-(methylsulfonyl)phenyl]methyl]-7',8'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclobutane-1,9'(6'*H*)-[4*H*]pyrido[1,2-*a*]pyrimidine]-2'-carboxamide;

15 *N*-[[2-[(dimethylamino)sulfonyl]-4-fluorophenyl]methyl]-7',8'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclobutane-1,9'(6'*H*)-[4*H*]pyrido[1,2-*a*]pyrimidine]-2'-carboxamide;

20 7',8'-dihydro-3'-hydroxy-4'-oxo-*N*-[[2-(tetrahydro-1,1-dioxido-2*H*-1,2-thiazin-2-yl)phenyl]methyl]-spiro[cyclobutane-1,9'(6'*H*)-[4*H*]pyrido[1,2-*a*]pyrimidine]-2'-carboxamide;

N-[(4-fluorophenyl)methyl]-6',7'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclopentane-1,8'(4'*H*)-pyrrolo[1,2-*a*]pyrimidine]-2'-carboxamide;

25

N-[[4-fluoro-2-(methylsulfonyl)phenyl]methyl]-6',7'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclopentane-1,8'(4'*H*)-pyrrolo[1,2-*a*]pyrimidine]-2'-carboxamide;

30 *N*-[[2-[(dimethylamino)sulfonyl]-4-fluorophenyl]methyl]-6',7'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclopentane-1,8'(4'*H*)-pyrrolo[1,2-*a*]pyrimidine]-2'-carboxamide;

N-[[4-fluoro-2-(1*H*-1,2,4-triazol-1-yl)phenyl]methyl]-6',7'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclopentane-1,8'(4'*H*)-pyrrolo[1,2-*a*]pyrimidine]-2'-carboxamide;

- 5 *N*-[(4-fluorophenyl)methyl]-2,3,5,6,7',8'-hexahydro-3'-hydroxy-4'-oxo-spiro[4*H*-pyran-4,9'(6'*H*)-[4*H*]pyrido[1,2-*a*]pyrimidine]-2'-carboxamide;

N-(phenylmethyl)-6',7'-dihydro-3'-hydroxy-4'-oxo- spiro[cyclopentane-1,9'(4'*H*)-pyrimido[2,1-*c*][1,4]oxazine]-2'-carboxamide;

10

N-[(4-fluorophenyl)methyl]-6',7'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclopentane-1,9'(4'*H*)-pyrimido[2,1-*c*][1,4]oxazine]-2'-carboxamide;

- 15 *N*-[(4-fluoro-3-methylphenyl)methyl]-6',7'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclopentane-1,9'(4'*H*)-pyrimido[2,1-*c*][1,4]oxazine]-2'-carboxamide;

N-[[4-fluoro-2-(1*H*-1,2,4-triazol-1-yl)phenyl]methyl]-6',7'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclopentane-1,9'(4'*H*)-pyrimido[2,1-*c*][1,4]oxazine]-2'-carboxamide;

20

N-[[4-fluoro-2-(methylthio)phenyl]methyl]-6',7'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclopentane-1,9'(4'*H*)-pyrimido[2,1-*c*][1,4]oxazine]-2'-carboxamide;

- 25 6',7'-dihydro-3'-hydroxy-*N*-[(4-methylphenyl)methyl]-4'-oxo-spiro[cyclopentane-1,9'(4'*H*)-pyrimido[2,1-*c*][1,4]oxazine]-2'-carboxamide;

N-[(4-chlorophenyl)methyl]-6',7'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclopentane-1,9'(4'*H*)-pyrimido[2,1-*c*][1,4]oxazine]-2'-carboxamide;

- 30 *N*-[(3,4-dichlorophenyl)methyl]-6',7'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclopentane-1,9'(4'*H*)-pyrimido[2,1-*c*][1,4]oxazine]-2'-carboxamide;

N-[(3,4-dimethylphenyl)methyl]-6',7'-dihydro-3'-hydroxy-4'-oxo-
spiro[cyclopentane-1,9'(4'H)-pyrimido[2,1-c][1,4]oxazine]-2'-carboxamide;

5 6',7'-dihydro-3'-hydroxy-N-[(4-methoxyphenyl)methyl]-4'-oxo-
spiro[cyclopentane-1,9'(4'H)-pyrimido[2,1-c][1,4]oxazine]-2'-carboxamide;

N-[(2-fluorophenyl)methyl]-6',7'-dihydro-3'-hydroxy-4'-oxo-
spiro[cyclopentane-1,9'(4'H)-pyrimido[2,1-c][1,4]oxazine]-2'-carboxamide;

10 N-[(2,4-dimethoxyphenyl)methyl]-6',7'-dihydro-3'-hydroxy-4'-oxo-
spiro[cyclopentane-1,9'(4'H)-pyrimido[2,1-c][1,4]oxazine]-2'-carboxamide;

N-[(3-fluorophenyl)methyl]-6',7'-dihydro-3'-hydroxy-4'-oxo-
spiro[cyclopentane-1,9'(4'H)-pyrimido[2,1-c][1,4]oxazine]-2'-carboxamide;

15

N-[(3-fluoro-4-methylphenyl)methyl]-6',7'-dihydro-3'-hydroxy-4'-oxo-
spiro[cyclopentane-1,9'(4'H)-pyrimido[2,1-c][1,4]oxazine]-2'-carboxamide;

20 N-[[2-(dimethylamino)sulfonyl]-4-fluorophenyl)methyl]-6',7'-dihydro-3'-
hydroxy-4'-oxo-spiro[cyclopentane-1,9'(4'H)-pyrimido[2,1-c][1,4]oxazine]-2'-
carboxamide;

25 N-[[5-fluoro-2-(1*H*-1,2,4-triazol-1-yl)phenyl]methyl]-6',7'-dihydro-3'-
hydroxy-4'-oxo-spiro[cyclopentane-1,9'(4'*H*)-pyrimido[2,1-c][1,4]oxazine]-2'-
carboxamide;

N-[2-(4-fluorophenyl)ethyl]-6',7'-dihydro-3'-hydroxy-4'-oxo-
spiro[cyclopentane-1,9'(4'*H*)-pyrimido[2,1-c][1,4]oxazine]-2'-carboxamide;

30 N-[3-(4-fluorophenyl)propyl]-6',7'-dihydro-3'-hydroxy-4'-oxo-
spiro[cyclopentane-1,9'(4'*H*)-pyrimido[2,1-c][1,4]oxazine]-2'-carboxamide;

N-[[4-fluoro-2-(5-methyl-1*H*-1,2,4-triazol-1-yl)phenyl]methyl]-6',7'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclopentane-1,9'(4'*H*)-pyrimido[2,1-*c*][1,4]oxazine]-2'-carboxamide;

5 6',7'-dihydro-3'-hydroxy-4'-oxo-*N*-[[2-(1*H*-1,2,4-triazol-1-yl)phenyl]methyl]-spiro[cyclopentane-1,9'(4'*H*)-pyrimido[2,1-*c*][1,4]oxazine]-2'-carboxamide;

N-[[4-fluoro-2-(tetrahydro-1,1-dioxido-2*H*-1,2-thiazin-2-yl)phenyl]methyl]-6',7'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclopentane-1,9'(4'*H*)-pyrimido[2,1-
10 *c*][1,4]oxazine]-2'-carboxamide;

6',7'-dihydro-3'-hydroxy-4'-oxo-*N*-[[2-(tetrahydro-1,1-dioxido-2*H*-1,2-thiazin-2-yl)phenyl]methyl]-spiro[cyclopentane-1,9'(4'*H*)-pyrimido[2,1-*c*][1,4]oxazine]-2'-carboxamide;

15 *N*-[(4-fluorophenyl)methyl]-6',7'-dihydro-3'-hydroxy-4'-oxo-spiro[piperidine-4,9'(4'*H*)-pyrimido[2,1-*c*][1,4]oxazine]-2'-carboxamide

N-[[4-fluoro-2-(methylsulfonyl)phenyl]methyl]-6',7'-dihydro-3'-hydroxy-4'-
20 oxo-spiro[cyclopentane-1,9'(4'*H*)-pyrimido[2,1-*c*][1,4]oxazine]-2'-carboxamide;

N-[[4-fluoro-2-(methylsulfonyl)phenyl]methyl]-4,5,6,7'-tetrahydro-3'-hydroxy-4'-oxo-spiro[furan-3(2*H*),9'(4'*H*)-pyrimido[2,1-*c*][1,4]oxazine]-2'-carboxamide; and

25 *N*-[[4-fluoro-2-[(methylamino)carbonyl]phenyl]methyl]-6',7'-dihydro-3'-hydroxy-4'-oxo-spiro[cyclobutane-1,9'(4'*H*)-pyrimido[2,1-*c*][1,4]oxazine]-2'-carboxamide;

30 or a pharmaceutically acceptable salt or solvate thereof.

8. A composition comprising a therapeutic amount of a compound of Claim 1 and a pharmaceutically acceptable carrier.

9. A method of inhibiting HIV integrase comprising contacting a compound of Claim 1 with HIV integrase.
10. A method of inhibiting HIV viral DNA integration into human DNA
5 comprising administering an effective amount of a compound of Claim 1 to a patient infected with HIV.
11. A method for treating HIV infection comprising administering a therapeutically effective amount of a compound of Claim 1, or a pharmaceutically
10 acceptable salt or solvate thereof, to a patient infected with HIV.
12. The method of claim 11, further comprising a therapeutically effective amount of one or more other HIV treatment agents selected from the group consisting of HIV protease inhibitors, HIV nucleoside reverse transcriptase inhibitors, HIV non-
15 nucleoside reverse transcriptase inhibitors, HIV-entry inhibitors, HIV integrase inhibitors, immunomodulators, or a combination thereof.