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72	FULL NAME(S) OF INVENTOR(S)

NAIDU, B. Narasimhulu

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HIV integrase inhibitors: cyclic pyrimidinone compounds

57	ABSTRACT (NOT MORE THAN 150 WORDS)

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The sheet(s) containing the abstract is/are attached.

If no classification is furnished, Form P.9 should accompany this form.
The figure of the drawing to which the abstract refers is attached.

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(71) Applicant (*for all designated States except US*): **BRISTOL-MYERS SQUIBB COMPANY** [US/US]; Route 206 and Province Line Road, Princeton, New Jersey 08543-4000 (US).

(72) Inventor; and
(75) Inventor/Applicant (*for US only*): **NAIDU, B. Narasimhulu** [IN/US]; 12 Skeetfield Point Road, Durham, Connecticut 06422 (US).

(74) Agents: **EPPERSON, James** et al.; Bristol-Myers Squibb Company, P.O. Box 4000, Princeton, NJ 08543-4000 (US).

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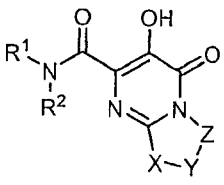
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(54) Title: HIV INTEGRASE INHIBITORS: CYCLIC PYRIMIDINONE COMPOUNDS



(I)

(57) Abstract: 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. Formula (I).

HIV INTEGRASE INHIBITORS: CYCLIC PYRIMIDINONE COMPOUNDS

CROSS REFERENCE TO RELATED APPLICATIONS

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

BACKGROUND OF THE INVENTION

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 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.

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 abacavir are nucleoside reverse transcriptase inhibitors that behave as substrate mimics to halt viral cDNA synthesis. And nevaripine, 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 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).

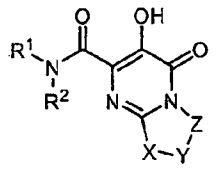
Unfortunately, not all patients are responsive and a large number fail this therapy. In fact, approximately 30-50% of patients ultimately fail combination therapy. Treatment failure in most cases is caused by the emergence of viral resistance. Viral resistance in turn is caused by the rapid turnover 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 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. 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.

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 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).

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:

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

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

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;

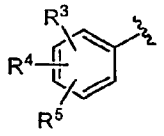
R^4 is hydrogen, halo, hydroxy, cyano, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}haloalkyl, or C_{1-6}haloalkoxy;

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

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^1 is 

;

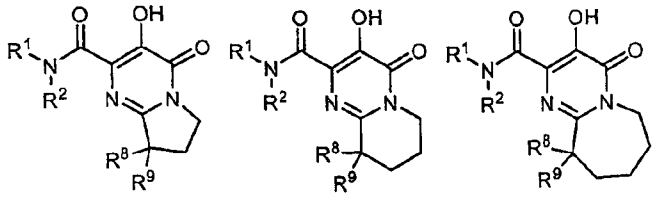
Ar^2 is tetrazolyl, triazolyl, imidazolyl, pyrazolyl, pyrrolyl, or dioxothiazinyl, and is substituted with 0-2 substituents selected from the group consisting of amino, oxo, halo, cyano, and C_{1-6}alkyl; and

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.

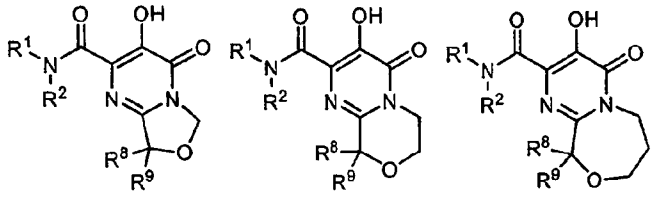
Another aspect of the invention is a compound of Formula I where X-Y-Z is $C(R^8)(R^9)CH_2CH_2$, $C(R^8)(R^9)CH_2CH_2CH_2$, or $C(R^8)(R^9)CH_2CH_2CH_2CH_2$.

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



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 $C(R^8)(R^9)OCH_2CH_2CH_2$.

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



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 $CH_2CH_2N(R^6)CH_2CH_2$.

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

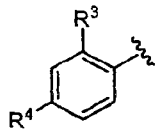
Another aspect of the invention is a compound of Formula I where R^2 is hydrogen.

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.

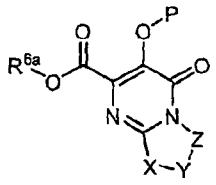
Another aspect of the invention is a compound of Formula I where R^5 is hydrogen.

Another aspect of the invention is a compound of Formula I where Ar^1 is



For a compound of Formula I, any scope of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8 and R^9 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, C_{1-6}alkyl, $C_{1-6}(Ar^1)$alkyl, ArC_{1-6}, C-(C=C)n-C, C_{1-6}-O-C_{1-6}-O-C_{1-6}, C_{1-6}-O-C_{1-6}-Ar, $C(Ar)_{2-3}$, $CO(C_{1-6})_{1-3}$, or COAr; and

P is hydrogen, mesyl, tosyl, allyl, benzyl, fluorenylmethyl, allyloxycarbonyl, benzyloxycarbonyl, fluorenylmethoxycarbonyl, tri(C_{1-6}alkyl)silyl, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, or C_{1-6}alkoxycarbonyl, ArC_{1-6}, C-(C=C)n-C, C_{1-6}-O-C_{1-6}-O-C_{1-6}, C_{1-6}-O-C_{1-6}-Ar, $CO(C_{1-6})_{1-3}$, COAr, or $C(Ar)_{2-3}$.

Another aspect of the invention is a compound of Formula II where R^{6a} is hydrogen, C_{1-6}alkyl, or $C_{1-6}(Ar^1)$alkyl; and P is hydrogen, mesyl, tosyl, allyl, benzyl,

fluorenylmethyl, allyloxycarbonyl, benzyloxycarbonyl, fluorenylmethoxycarbonyl, tri(C_{1-6}alkyl)silyl C_{1-6}alkyl, C_{1-6}alkylcarbonyl, or C_{1-6}alkoxycarbonyl.

Some compounds of the invention are

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;

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;

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;

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;

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;

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;

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;

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;

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;

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;

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;

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-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;

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;

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-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;

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'-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;

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;

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;

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;

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;

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;

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;

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

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;

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-(1H-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-[[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;

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;

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;

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;

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;

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;

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;

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;

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;

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-*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;

N-[(4-fluorophenyl)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;

N-[(4-fluoro-3-methylphenyl)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;

N-[[4-fluoro-2-(1H-1,2,4-triazol-1-yl)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;

N-[[4-fluoro-2-(methylthio)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;

N-[(4-fluorophenyl)methyl]-2,3,5,6,6',7'-hexahydro-3'-hydroxy-4'-oxo-spiro[4H-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]-2,3,5,6,6',7'-hexahydro-3'-hydroxy-4'-oxo-spiro[4H-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;

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;

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;

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;

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;

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;

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;

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;

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;

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;

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-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;

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-(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;

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;

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'-oxo-spiro[cyclopentane-1,9'(4'H)-pyrimido[2,1-c][1,4]oxazine]-2'-carboxamide;

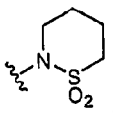
N-[[4-fluoro-2-(methylsulfonyl)phenyl]methyl]-4,5,6',7'-tetrahydro-3'-hydroxy-4'-oxo-spiro[furan-3(2H),9'(4'H)-pyrimido[2,1-c][1,4]oxazine]-2'-carboxamide; and

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.

"Alkyl," "alkoxy," "haloalkyl," and related terms for other hydrocarbon and substituted hydrocarbon substituents include straight and branched isomeric configurations. A term such as "C_{1-6}(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

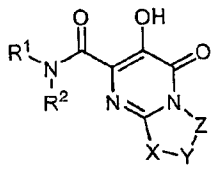
carbocyclic and heterocyclic systems. Some substituents are divalent, for example, X-Y-Z. Divalent substituents which are asymmetric can be attached to the parent molecule in either of the configurations.

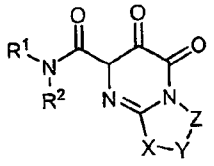
"Dioxothiazinyl" means .

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.

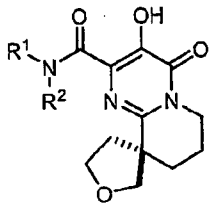
The invention also includes all solvated forms of the compounds, particularly hydrates. Solvates do not contribute significantly to the physiological activity or toxicity of the compounds and as such function as pharmacological equivalents. Solvates may form in stoichiometric amounts or may form from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

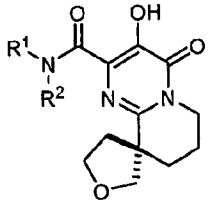
The invention includes all tautomeric forms of the compounds. An example of a tautomeric pair is shown below.





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

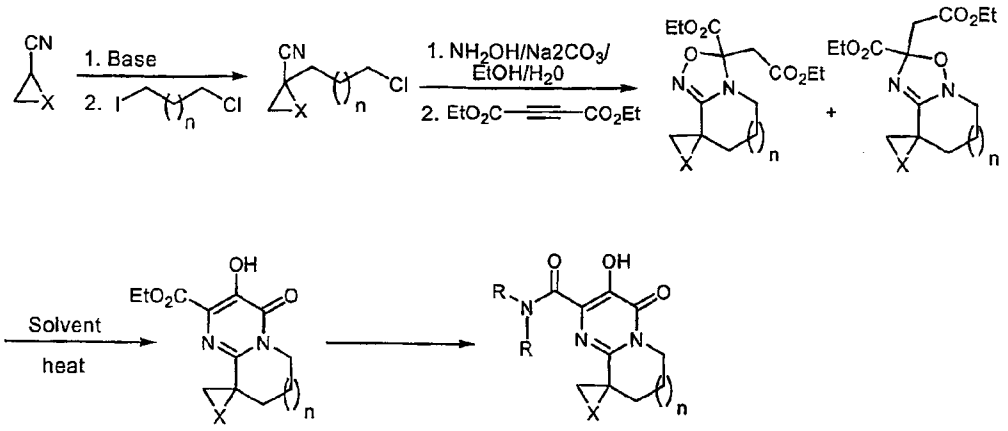




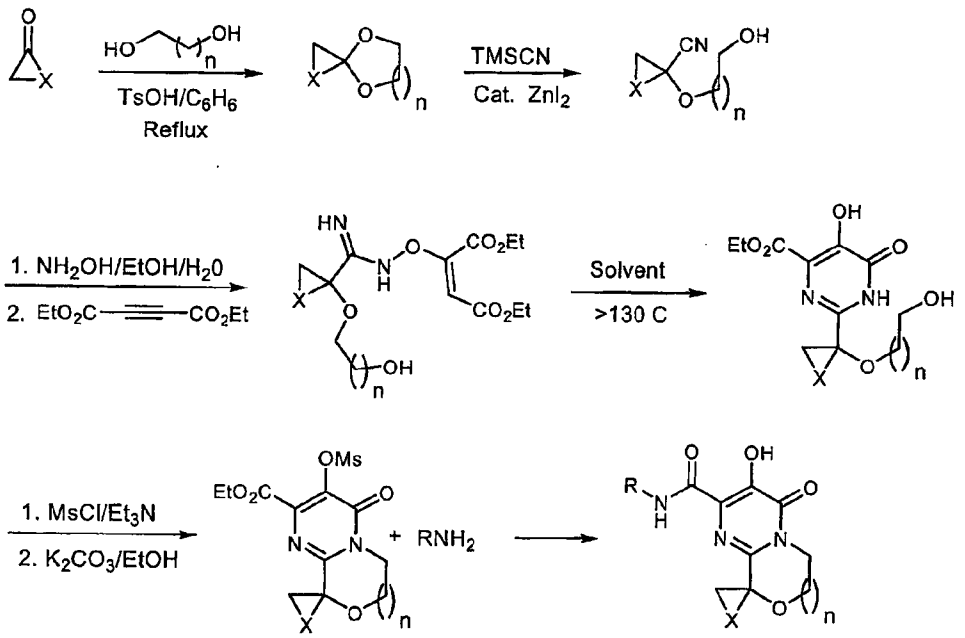
Synthetic Methods

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.

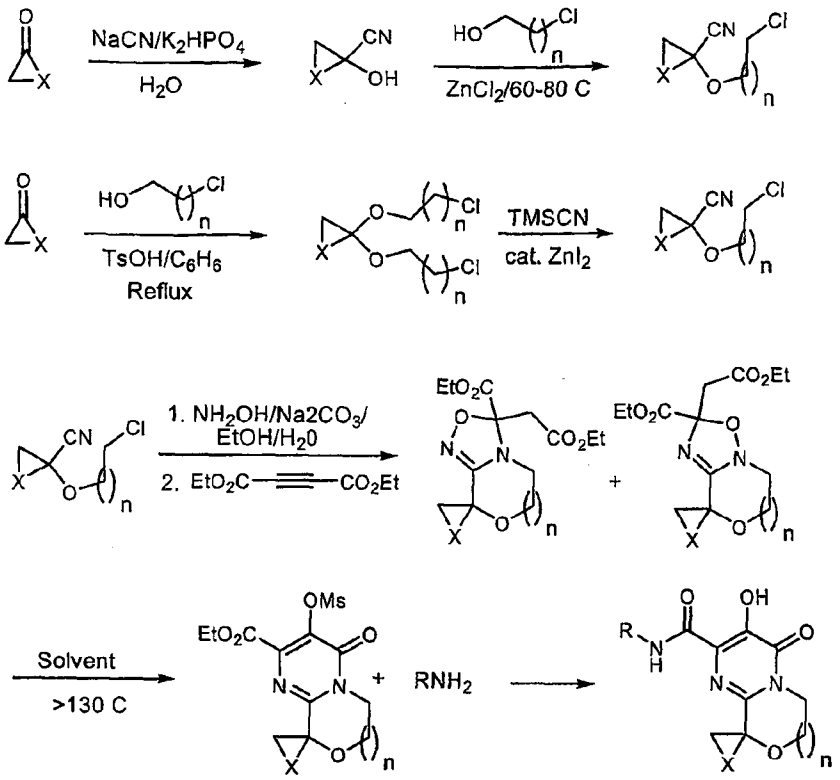
Scheme 1.



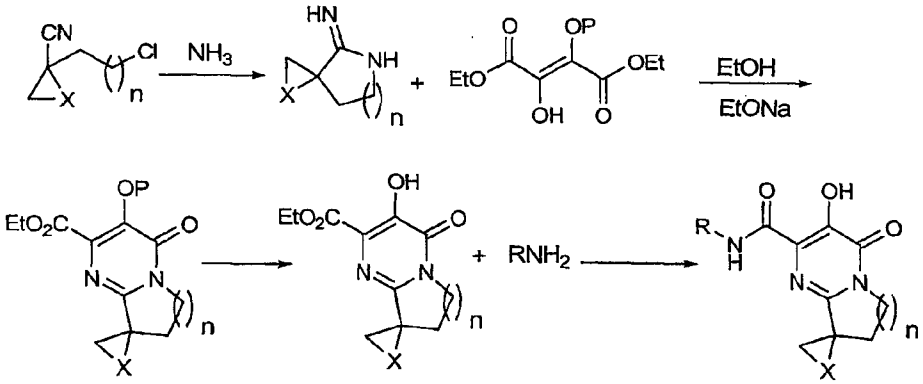
Scheme 2.



Scheme 3.



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 IC_{50} 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 μM; B: 0.01-0.1 μM.

Pharmaceutical Composition and Methods of Use

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).

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 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.

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.

"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.

"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 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.

"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 exipients. 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, losenges, 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.

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
HBY097 (non-nucleoside reverse transcriptaseinhibitor)	Hoechst Marion Roussel	HIV infection, AIDS, ARC
Hypericin	VIMRx Pharm.	HIV infection, AIDS, ARC
Recombinant Human Interferon Beta	Triton Biosciences (Almeda, 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 Ingleheim	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 & CMVinfections
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

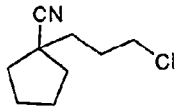
ANTI-INFECTIVES

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

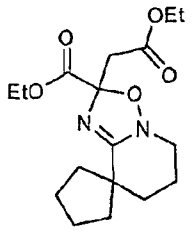
DESCRIPTION OF SPECIFIC EMBODIMENTS

Intermediate **1**



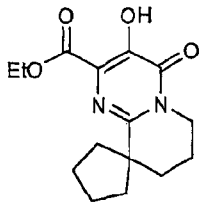
1-(3-chloropropyl)cyclopentanecarbonitrile. To a stirred solution of cyclopentanecarbonitrile (1.04 mL, 10 mmol) in THF (20 mL) at -78 °C was added LiHMDS (1M in THF, 11 mL) via syringe. After 30 min, 1-chloro-3-iodopropane (1.6 mL, 15 mmol) was added at once and slowly warmed to room temperature. After 20 h, the reaction mixture was quenched with saturated ammonium chloride (1 mL), diluted with EtOAc (100 mL), dried ($MgSO_4$), filtered and concentrated to give intermediate 1 as yellow oil which was used in the next step without further purification.

Intermediate 2



To a stirred mixture of intermediate 1 from previous experiment and 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 was diluted with water (50 mL) and extracted with EtOAc (3 X 50 mL). The combined EtOAc extracts dried (Na_2SO_4), 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, $CDCl_3$) 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 (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 $C_{17}H_{27}N_2O_5$: 339.1920; found: 339.1923.

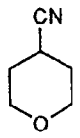
Intermediate 3



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

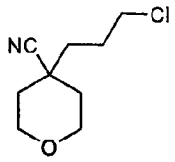
containing 0.1% TFA (gradient elution). The fractions containing the product were combined and concentrated to afford intermediate **3** as a dark paste (0.8639 g, 28.6%). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 10.75 (1H, br s), 4.43 (2H, q, J = 7.0 Hz), 4.03 (2H, t, J = 5.8 Hz), 2.25-2.20 (2H, m), 1.99-1.93 (4H, m), 1.79-1.64 (6H, m), 1.42 (3H, t, J = 7.0 Hz), . HRMS (M+H) calcd for $C_{15}H_{21}N_2O_4$: 293.1501; found: 293.1513.

Intermediate **4**



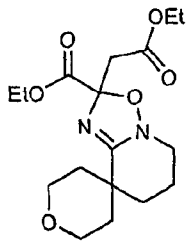
Tetrahydro-2H-pyran-4-carbonitrile. A solution of tetrahydro-4*H*-pyran-4-one (25 g, 250 mmol) and toluenesulfonylmethyl cyanide (53.7 g, 275 mmol) dissolved in ethylene glycol dimethylether (1 L) was cooled to 0 °C. Added dropwise over 30 min was a solution of potassium t-butoxide (56 g, 500 mmol) dissolved 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 $NaHCO_3$. The organic phase was dried (Na_2SO_4) 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). ^{1}H NMR (300 MHz, $CDCl_3$) 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).

Intermediate **5**



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 (Na_2SO_4), 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%). ^{1}H NMR (500 MHz, $CDCl_3$) 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).

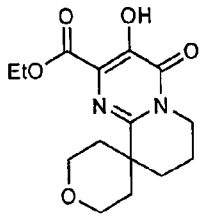
Intermediate **6**



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 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 (Na_2SO_4), 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%%). ^{1}H NMR (500 MHz, $CDCl_3$) δ:. HRMS (M+H) calcd for $C_{17}H_{27}N_2O_5$:; found. ^{1}H NMR (500 MHz, $CDCl_3$) 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,

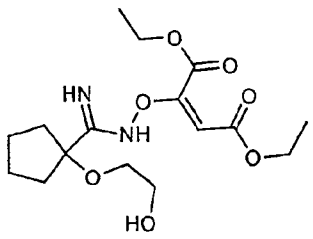
m), 3.26 (1H, d, J_{AB} = 16.2 Hz), 2.97 (1H, d, J_{AB} = 16.2 Hz), 2.06-1.89 (4H, m), 1.66-1.66 (2H, m), 1.60-1.53 (2H, m), 1.30 (3H, t, J = 7.0 Hz), 1.24 (3H, t, J = 7.0 Hz).

Intermediate 7



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%). ^{1}H 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 (M+H) calcd for $C_{15}H_{21}N_2O_4$: 309.1451; found: 309.1463.

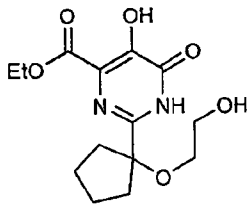
Intermediate 8



(E)-2-{[1-(2-Hydroxyethoxy)cyclopentanecarboximidoyl]-aminooxy}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.

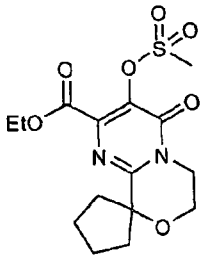
After 16 h, EtOH (100 mL) followed by 50% aqueous hydroxylamine (6.43 mL, 100 mmol) was added and stirred at 80 °C for 2 h. Then, the reaction mixture was cooled in ice-water bath and diethyl acetylenedicarboxylate (16 mL, 100 mmol) was added over 5 min. Then, cooled bath removed, stirred for 4 h at 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 $C_{16}H_{27}N_2O_7$: 359.2; found: 359.2.

Intermediate **9**



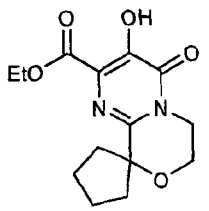
5-Hydroxy-2-[3-(2-hydroxy-ethoxy)tetrahydrofuran-3-yl]-6-oxo-1,6-dihydropyrimidine-4-carboxylic acid ethyl ester. A xylenes (200 ml) solution of crude intermediate **8** (100 mmol) was heated at reflux for 24 h, cooled and concentrated. The resulting dark-residue was stirred with 0.5 M Na_2CO_3 (150 mL) for 30 min and extracted with EtOAc (3 X 50 mL). The combined organic phases were re-extracted with 0.5 M Na_2CO_3 (50 mL) and EtOAc extracts discarded. The combined aqueous layers was carefully acidified with conc. HCl (20 mL) and extracted with CH_2Cl_2 (4 X 50 mL). The combined CH_2Cl_2 layers dried (Na_2SO_4/actvated 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 $C_{14}H_{21}N_2O_6$: 313.32; found: 313.27.

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 (Na_2SO_4), filtered and concentrated to give viscous yellow oil. This oil was re-dissolved in anhydrous EtOH (100 mL) and stirred with K_2CO_3 (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, $CDCl_3$) δ: 4.43 (2H, q, J = 7.0 Hz), 3.99 (4H, s), 3.53 (3H, s), 2.33-2.28 (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 $C_{15}H_{21}N_2O_7S$: 373.1069; found: 373.1053.

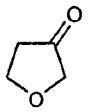
Intermediate **11**



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 CH_2Cl_2 (3 X

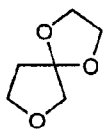
35 mL). The combined organic layers dried (Na2SO4), filtered and concentrated to give intermediate **11** as a brown solid (0.4668 g, 86%). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 10.49 (1H, s), 4.44 (2H, q, J = 7.0 Hz), 4.03-3.97 (4H, m), 2.28-2.22 (2H, m), 2.06-2.01 (2H, m), 1.93-1.81 (4H, m), 1.42 (3H, t, J = 7.0 Hz). HRMS (M+H) calcd for $C_{14}H_{19}N_2O_5$: 295.1294; found: 295.1293.

Intermediate **12**



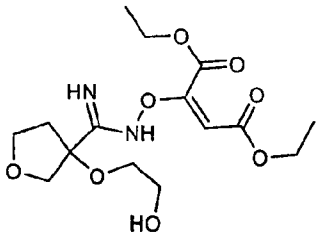
Dihydrofuran-3(2H)-one . A mixture of 3-hydroxyfuran (24 g, 272 mmol) and TEMPO (0.86 g, 5.5 mmol) in CH_2Cl_2 (175 mL) and KBr (7.141 g, 60 mmol) in water was vigorously stirred and cooled in an ice-water bath. The pH of NaOCl (commercial grade bleach, 600 mL, 806 mmol) was adjusted to 9.5 by dissolving $NaHCO_3$ (8.632 g, 102.75 mmol) immediately before use. This NaOCl solution was 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 CH_2Cl_2 (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. Na_2CO_3 (2 X 150 mL). The organic layer dried (Na2SO4), filtered and concentrated to give intermediate **12** as a pale yellow liquid (15.79 g, 67%) which was used without purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.24 (2H, t, J = 7.3 Hz), 3.86 (2H, s), 2.49 (2H, t, J = 7.3 Hz).

Intermediate **13**



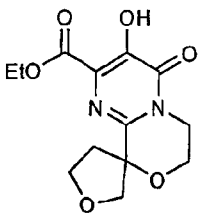
1,4,7-Trioxaspiro[4.4]nonane. A mixture of intermediate **12** (15.79 g, 183.5 mmol), ethylene glycol (16.7 mL, 300 mmol) and cat. $TsOH•H_2O$ (100 mg) in benzene (100 mL) was heated at reflux using Dean-Stark trap. After 17 h, the reaction mixture was cooled, diluted with ether (150 mL), washed with sat. Na_2CO_3 and brine (50 mL each), dried (Na_2SO_4), 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, $CDCl_3$) 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).

Intermediate **14**



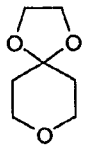
(E)-2-{[3-(2-Hydroxy-ethoxy)tetrahydrofuran-3-carboximidoyl]-aminooxy}but-2-enedioic acid diethyl ester. Prepared according to the procedure for intermediate **8**. Yield: 38%; viscous yellow paste. ^1H NMR (500 MHz, $CDCl_3$) δ: 5.78 (1H, d, J = 7.6 Hz), 5.59 (1H, br s), 5.38 (1H, s), 4.37-4.27 (2H, 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 $C_{15}H_{25}N_2O_8$: 361.1611; found: 361.1620.

Intermediate **15**



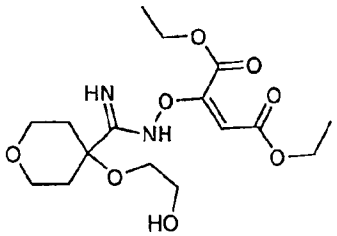
Prepared according to the procedure for intermediate **11**. Yield: 29%; brown solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 10.63 (1H, br s), 4.44 (2H, q, J = 7.0 Hz), 4.18-4.11 (4H, m), 4.08-4.01 (4H, m), 2.66-2.60 (1H, m), 2.35-2.30 (1H, m), 1.41 (3H, t, J = 7.0 Hz). HRMS (M+H) calcd for $C_{13}H_{17}N_2O_6$: 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). ^{1}H-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).

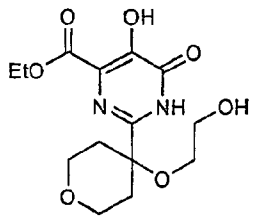
Intermediate **17**



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

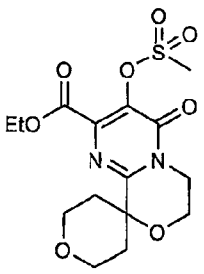
J = 22.7 Hz), 5.50 (1H, bs), 5.29 (1H, bs), 4.33-4.23 (2H, m), 4.19-4.04 (2H, m), 3.95-3.87 (1H, m), 3.79-3.63 (6H, m), 3.43-3.39 (2H, m), 2.15-1.74 (4H, m), 1.35-1.19 (6H, m). LCMS $[M+H]^+$ calcd for $C_{16}H_{27}N_2O_8$: 375.17; found: 375.19.

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.

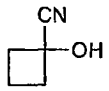
Intermediate **19**



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

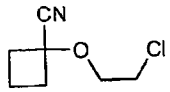
by slow addition of triethylamine (1.07 mL, 7.9 mmol). The mixture stirred for 4 h while gradually warming to room temp. before diluting with EtOAc. The mixture was washed with water and brine and dried (Na_2SO_4) before concentrating to give a dark oil. This was dissolved in EtOH (20 mL) and THF (10 mL) and added 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 %). ^{1}H-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, 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 $[M+H]^+$ calcd for $C_{15}H_{21}N_2O_8S_3$: 389.10; found: 389.13.

Intermediate **20**



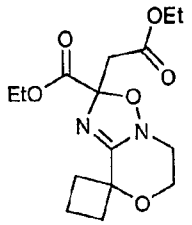
1-Hydroxycyclobutanecarbonitrile. To a flask containing cyclobutanone (13.41 g, 191 mmol) was added a solution of potassium phosphate monobasic (29.10 g, 214 mmol) in water (50 mL), followed by a solution of sodium cyanide (10.39 g, 210 mmol) in water (50 mL), and the reaction was stirred for 16 hours. 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 approximately 15% of intermediate **20**. The intermediate was used without further purification or treatment. ^{1}H 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**



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 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. ^{1}H NMR (500 MHz, $CDCl_3$) 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).

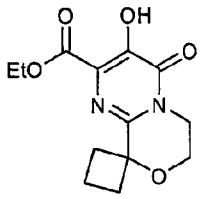
Intermediate **22**



A solution of intermediate **21** (2.64 g, 16.5 mmol) in ethanol (10 mL) was 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 $[M+H]^+ = 327.14$.

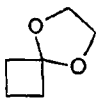
Intermediate **23**



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. ^{1}H 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 $[M+H]^+ = 281.11$.

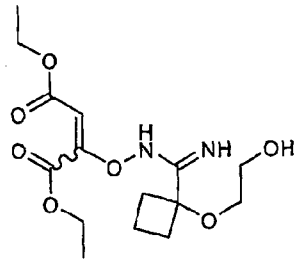
Alternative preparation of intermediate **23** from cyclobutanone.

Intermediate **24**



5,8-Dioxa-spiro[3.4]octane. A solution of cyclobutanone (7.7 g, 0.11 mol), 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: ^{1}H NMR ($CDCl_3$, 500 MHz) δppm 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**

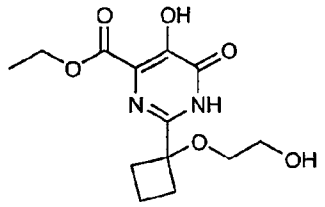


2-{[1-(2-hydroxyethoxy)cyclobutanecarboximidoyl]-aminooxy}but-2-enedioic acid diethyl ester. To a mixture of intermediate **24** (5.70 g, 50 mmol) and trimethylsilyl cyanide (5.05 g, 50 mmol) was added a catalytic amount of ZnI_2 (12 mg) in a cool water bath of ~10°C and the mixture stirred at room temperature for 5 hrs to obtain 10.7 g of 1-(2-trimethylsilanyloxyethoxy)cyclobutanecarbonitrile as a mobile oil: ^{1}H 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) δppm 120.43 (CN), 72.05

(C), 67.71 (CH_2), 61.49 (CH_2), 34.02 (CH_2), 12.91 (CH_2), -0.29 (CH_3). LC/MS m/z 142 (M+H-$SiMe_3$).

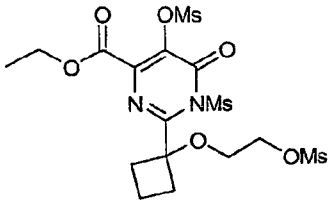
A solution of 1-(2-trimethylsilanyloxyethoxy)cyclobutanecarbonitrile (3.5 g, 16.4 mmol) and 50 % aqueous hydroxylamine (1.08 g, 16.4 mmol) in EtOH (16 mL) was stirred in an oil bath heated at 80°C for 2.5 hrs and then cooled to room temperature. To a solution was added drop-wise diethyl acetylenedicarboxylate (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, $CDCl_3$) 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 $C_{15}H_{25}N_2O_7$ 345.1662, found 345.1648.

Intermediate **26**



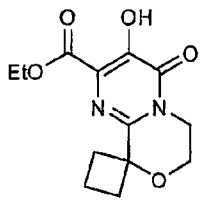
5-hydroxy-2-[1-(2-hydroxy-ethoxy)-cyclobutyl]-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid ethyl ester. A solution of a crude intermediate **25** (5.9 g) in xylenes (30 mL) was heated at 150-155 °C for 20 h. The mixture was concentrated in vacuo and the residue re-dissolved in EtOAc (30 mL) was extracted 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 CH_2Cl_2 (2x20 ml). The combined organic extracts were dried (Na_2SO_4), 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



Ethyl 1-(methylsulfonyl)-5-(methylsulfonyloxy)-2-(1-(2-(methylsulfonyloxy)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 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. ^{1}H NMR (500 MHz, $CDCl_3$) δ:4.49 (2H, q, J = 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.

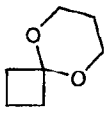
Intermediate 28



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

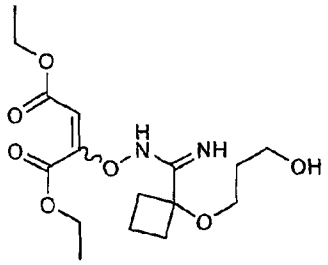
mL) and extracted with ethyl acetate (2 x 100 mL). The aqueous layer was made acidic (pH ~ 1-2) using 6.0 N hydrochloric acid, and the resulting solid was extracted with ethyl acetate (2 x 75 mL). The combined extract was dried (sodium sulfate), filtered to remove solids, and concentrated to give intermediate **28** (4.30 g, 61%) as a light brown solid. ^{1}H NMR (500 MHz, $CDCl_3$) 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). ^{13}C NMR (126 MHz, $CDCl_3$) 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.

Intermediate **29**



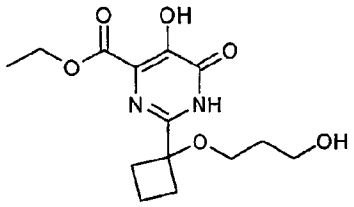
Intermediate **29** was prepared (50% yield) according to the procedure for intermediate **24**. ^{1}H NMR (500 MHz, C_6D_6) δ: 3.49 (4H, t, J=5.5 Hz), 2.23 (4H, t, J=8 Hz), 1.63 (2H, qt, J=8 Hz), 1.24 (2H, qt, J=5.5 Hz).

Intermediate **30**



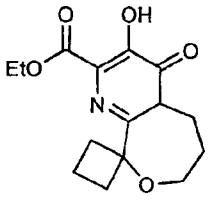
Intermediate **30** was prepared (52% yield) according to the procedure for intermediate **25**. ^{1}H NMR (500 MHz, C_6D_6) δ: 3.54 (2H, t, J=6.1 Hz), 3.45 (2H, t, J=6.1 Hz), 2.06 - 2.12 (2H, m), 1.87 (2H, dq, J=9.7, 2.6 Hz), 1.68 (2H, qt, J=6.1 Hz), 1.43 - 1.51 (1H, m), 1.26 - 1.34 (1H, m), 0.10 (9H, s). LC/MS $[M+H]^+$ = 359.20

Intermediate **31**



Intermediate **31** was prepared (69% yield) according to the procedure for intermediate **26**. ^{1}H 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) $[M+H]^+$ = 313.05.

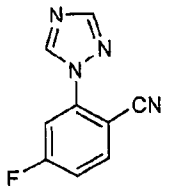
Intermediate **32**

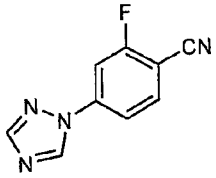


A cold (0°C) solution of intermediate **31** (3.0 g, 9.6 mmol) in tetrahydrofuran (25 mL) was treated with methanesulfony chloride (3.30 g, 29 mmol) followed by dropwise addition of triethylamine (4.7 mL, 33.6 mmol). The reaction was stirred for 16 hours at room temperature. The solvent was removed *in 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. ^{1}H NMR

(500 MHz, $CDCl_3$) 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).

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



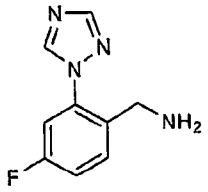


4-Fluoro-2-(1H-1,2,4-triazol-1-yl)benzonitrile (33) and 4-(1H-1,2,4-triazol-1-yl)-2-fluorobenzonitrile. To a solution of 2,4-difluorobenzonitrile (10 g, 72 mmol) dissolved in THF (20 mL), and DMF (40 mL) was added 1,2,4-triazole sodium derivative (6.3 g, 70 mmol) and the mixture was stirred at 90 °C 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%).

Intermediate **33**: ^{1}H NMR (500 MHz, $CDCl_3$) 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 $C_9H_6N_4F$: 189.05; found: 189.13.

Intermediate **34**: ^{1}H NMR (500 MHz, $CDCl_3$) 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 $C_9H_6N_4F$: 189.05; found: 189.13.

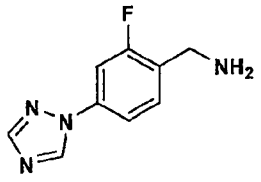
Intermediate **35**



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

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 H_2 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%). ^{1}H NMR (500 MHz, CD_3OD) 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 $C_9H_{10}N_4F$: 193.08; found: 193.16.

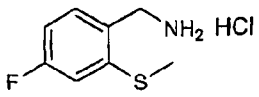
Intermediate **36**



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

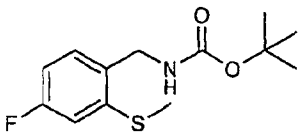
Intermediate **36** was prepared (79% yield) following the procedure for intermediate **35** using intermediate **34**. ^{1}H NMR (500 MHz, CD_3OD) δ: 9.25 (1H, s), 8.46 (1H, s), 7.80 (1H, dd, J = 8.6, 5.8 Hz), 7.64 (1H, dd, J = 8.8, 2.4 Hz), 7.44 (1H, td, J = 8.3, 2.6 Hz), 4.17 (2H, s). LCMS (M+H) calcd for $C_9H_{10}N_4F$: 193.08; found: 193.16.

Intermediate **37**



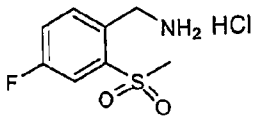
4-Fluoro-2-methylsulfanyl-benzylamine. 4-Fluoro-2-(methylthio)benzonitrile (prepared as in Anthony, N. J. et al. PCT Appl. WO 02/30931, 2002) (1.67 g, 0.1 mol) was dissolved in 20 mL THF and under N_2 treated with 10 mL 2M $BH_3.Me_2S$. This was heated at 60 °C for 2 hrs. Heating was discontinued and 5mL MeOH was cautiously added, followed by the cautious addition of 4 mL 6N HCl. Then 20 mL more H_2O added and EtOAc and the layers were separated. The aqueous layer was made basic with 1N NaOH and extracted with CH_2Cl_2. The extracts were dried ($MgSO_4$), filtered, concentrated and dried in vacuum to give intermediate **37** (1.3g, 76%)as a solid. ^{1}H NMR (500 MHz, $CDCl_3$) 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.

Intermediate **38**



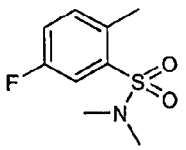
N-t-Butoxycarbonyl- (4-fluoro-2-(methylthio)phenyl)methanamine. A stirred solution of intermediate **37** (5.1g, 0.03 mol) and 3.3g triethylamine in 100mL CH_2Cl_2 under N2 was treated with di-t-butyl dicarbonate (7.2g, 0.033 mol) portionwise and stirred at room temperature for 30 min. Then, the reaction mixture was washed with dil HCl and water. The organic layer was dried over $MgSO_4$, filtered and concentrated to leave 8.1g (100%) of intermediate **38** as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) 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 (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 CH_2Cl_2. 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 CH_2Cl_2 and concentration of the extracts gave a gum which was treated with HCl in ethanol to give an additional 0.9g of intermediate **39**. ^{1}H NMR (500 MHz, DMSO-D_6) 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.

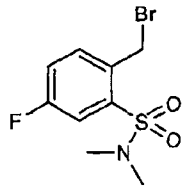
Intermediate **40**



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 drop-wise 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 (SiO_2, 5 % Et_2O in CH_2Cl_2) to obtain intermediate **40** (4.3 g, 90 %) as a clear oil. ^{1}HNMR (500 MHz, $CDCl_3$) δ: 2.57 (3 H, s) 2.82 (3 H, s) 2.82 (3 H, s)

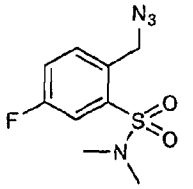
7.12 - 7.18 (1 H, m) 7.28 (1 H, dd, *J*=8.2, 5.5 Hz) 7.59 (1 H, dd, *J*=8.2, 2.1 Hz). LC/MC (M+H): 218.

Intermediate **41**



2-Bromomethyl-5-fluoro-N,N-dimethyl-benzenesulfonamide. 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. 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 %). ^{1}HNMR (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 - 7.65 (2 H, m). LC/MC (M+H): 296/298.

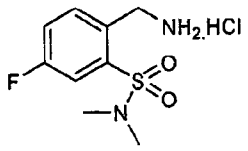
Intermediate **42**



2-Azidomethyl-5-fluoro-N,N-dimethyl-benzenesulfonamide. 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. ^{1}HNMR (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).

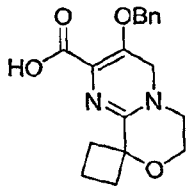
Intermediate **43**



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 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 and concentrated to obtain free amine **43** (210 mg, 35 %) as an oil. ^{1}H 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.

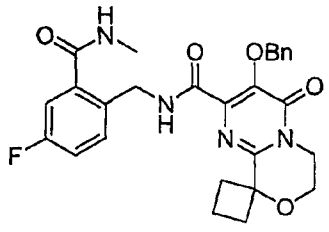
Alternatively, a solution of intermediate **42** (23.6 g, 91.37 mm0l) in EtOH (100 mL) and 5M aq. HCl (22 mL) was degassed by bubbling N2 through it for 5 min. and 10%Pd/carbon (2.0 g) was added. This mixture was evacuated and vented to H_2 (repeated three times) and left on Parr shaker for 20 h under H2 (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 organic layer discarded and aqueous layer freeze dried to afford 43 (16.3 g, 66%) as pale yellow powder.

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 (Na_2SO_4), 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: ^{1}H NMR (500 MHz, $CDCl_3$) 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).

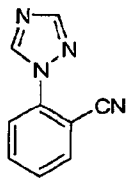
Intermediate **45**



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

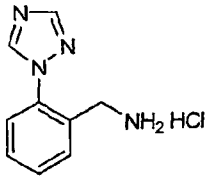
minutes. To this was added 2-(aminomethyl)-5-fluoro-N-methylbenzamide hydrochloride (prepared according to M. Egbertson et al PCT Appl. WO 03077850) and *N,N*-dimethylaminopyridine (0.068 g, 0.55 mmol) and the reaction was stirred for 16 hours. The solvent was removed *in vacuo* and the crude product in ethyl acetate (25 mL) was washed with 1.0 N hydrochloric acid (25 mL), then dried (Na_2SO_4), 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: ^{1}H NMR (500 MHz, $CDCl_3$) 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**



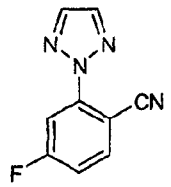
2-(1H-1,2,4-triazol-1-yl)benzonitrile: A suspension of 2-fluorobenzylnitrile (3.0 g, 25 mmol) and 1,2,4-triazole sodium complex (2.4 g, 27 mmol) were stirred in THF (7 mL) and DMF (14 mL) at 95° C for 18 h. After cooling and concentrating, the product was crystallized from hot CH_2Cl_2/hexane (1:1) to give the title compound as a white solid (4.25 g, 100% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) 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 $C_9H_7N_4$: 171.06; found: 171.12.

Intermediate **47**



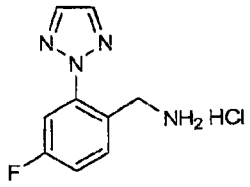
2-(1H-1,2,4-triazol-1-yl)phenyl)methanamine hydrochloride: Intermediate **46** (4.25 g, 25 mmol) was dissolved in EtOH (50 mL) and 1N HCl (25 mL). Added Pd/C (1 g) and mixture was shaken under H_2 for 2 h at 50 psi. After filtration over celite and concentration, the residue was triturated with diethyl ether and the title compound was collected as a white solid (3.94 g, 75% yield). ^{1}H-NMR (300 MHz, CD_3OD) δ: 9.01 (1H, s), 8.32 (1H, s), 7.78-7.64 (4H, m), 4.15 (2H, s). LCMS $[M+H]^+$ calcd for $C_9H_{11}N_4$: 175.09; found: 175.17.

Intermediate **48**



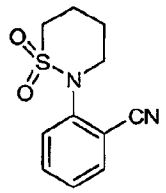
4-Fluoro-2(2H-1,2,3-triazol-2-yl)benzonitrile: To a solution of 1*H*-1,2,3-triazole (3.5 g, 50.7 mmol) in THF (10 mL) and DMF (20 mL) was added portionwise, NaH (1.3 g, 51 mmol, 95%). The mixture was stirred at room temp for 30 min. Added to this was 2,4-difluorobenzonitrile (7.6 g, 55 mmol) and the 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). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.92 (2H, s), 7.88-7.79 (2H, m), 7.19-7.12 (1H, m). LCMS $[M+H]^+$ calcd for $C_9H_6N_4F$: 189.05; found: 189.12.

Intermediate **49**



4-Fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)methanamine 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 H_2 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). ^{1}H-NMR (500 MHz, CD_3OD) δ: 8.13 (2H, s), 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 $C_9H_{10}N_4F$: 193.08; found: 193.16.

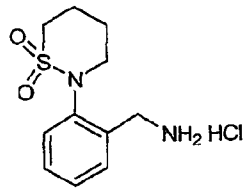
Intermediate **50**



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-Fluorobenzonitrile (3.37 mL, 31.3 mmol) was added and the micture 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 (Na_2SO_4) and concentrated. The residue was purified by flash chromatography eluting with 10%-100% EtOAc/hexane. The isolated solid was recrystalized from hot EtOAc/hexane (2:1) to give the title compound as white crystals (4.15 g, 70% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) 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.

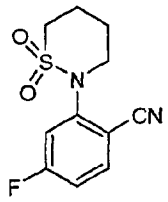
Intermediate **51**



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). ^{1}H-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.

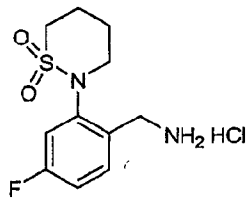
Intermediate **52**



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). ^{1}H-NMR (500 MHz, $CDCl_3$)

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.

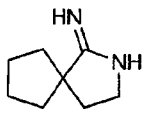
Intermediate **53**



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

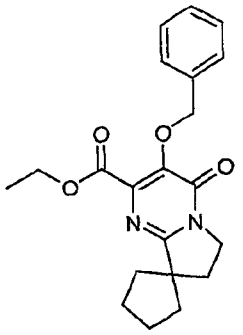
Following the procedure for Intermediate **51** using Intermediate **52** (1.37 g, 5.4 mmol) gave the title compound as a white solid (1.58 g, 100 % yield). ^{1}H-NMR (300 MHz, CD_3OD) δ: 7.61 (1H, dd, J = 8.4, 6.2 Hz), 7.38 (1H, dd, J = 9.3, 2.7 Hz), 7.28 (1H, td, J = 8.2, 2.7 Hz), 7.26 (2H, dd, J = 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 $C_{11}H_{16}N_2FO_2S$: 259.09; found: 259.24.

Intermediate **54**



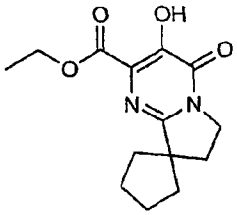
To a solution of 1-(2-chloroethyl)cyclopentanecarbonitrile (1.38g, 8.73 mmol; prepared according to R. M. Burk et al Heterocycles **1993**, *35*, 205) in 40 mL MeOH was added 1 mmol sodium iodide and the solution was saturated with ammonia. The reaction bottle was sealed and warmed at 90°C with stirring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

Intermediate **55**



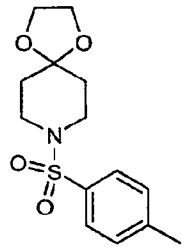
To a solution of diethyl-2-(benzyloxy)-3-hydroxyfumarate [prepared from benzyloxy ethylacetate (2.91g, 0.015 mol) and diethyloxalate (2.19g, .015 mol) with an equivalent amount of sodium hydride in 40 mL THF and 2 drops EtOH by stirring for 30 min] in 20 mL EtOH was added intermediate **54** in 10 mL EtOH and with stirring 60% NaH (300mg, 0.0075 mol) was added portionwise. This was stirred for 3 h at rt and concentrated. The residue was dissolved in CH_2Cl_2 and washed with water. The CH2Cl2 layer was dried over $MgSO_4$, filtered and concentrated. Chromatography on silica and elution with 9:1 CH_2Cl_2:Et_2O gave 600mg of the title compound **55** (Yield = 19%). LC/MS (M+H): 369. ^{1}H NMR (500 MHz, $CDCl_3$) 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), 2.04-2.17 (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**



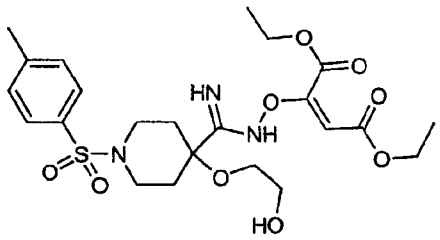
Intermediate **55** was dissolved in 15 mL TFA and stirred at rt for 16h. The TFA was removed and the crude chromatographed on C18 using 10% CH_3CN/ H_2O initially as eluant. Product eluted with 20% CH_3CN. Pure fractions were concentrated and extracted with CH_2Cl_2. Evaporation of the solvent left 300 mg (Yield = 51%) of the title compound **56**. LC/MS (M+H): 279. ^1H NMR (300 MHz, $CDCl_3$) 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**



To a solution of 1,4-dioxa-8-azaspiro[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 CH_2Cl_2. The resulting suspension was stirred at room temperature 5 h. and washed with saturated aqueous $NaHCO_3$, water and dried (Na_2SO_4). Concentration gave the Intermediate **57** as a white solid (20.20 g, 97%). ^1H-NMR (300 MHz, $CDCl_3$) 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 $C_{14}H_{20}NO_4S$: 298.11; found: 298.16.

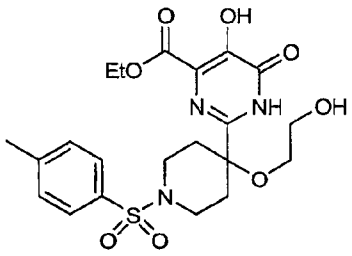
Intermediate **58**



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.

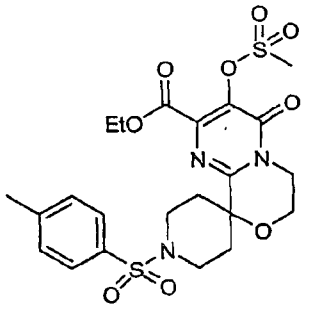
To solution of above crude in EtOH (60 mL) was added hydroxylamine (2.1 mL, 31.3 mmol, 50wt% in water) and the resulting mixture was stirred at room temperature. After 18 h diethylacetylenedicarboxylate (6.0 mL, 37.5 mmol) was added and stirred for additional 3 days and concentrated. The residue was purified by flash chromatography eluting with 0%-25%-50% EtOAc/Hexane to give the Intermediate **58** as a yellow foam (11.72 g, 71%). ^{1}H-NMR (300 MHz, $CDCl_3$) 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 $C_{23}H_{34}N_3O_9S$: 528.20; found: 528.13.

Intermediate **59**



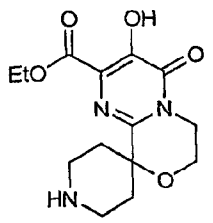
1,2,4-trimethylbenzene (100 mL) was added to Intermediate **58** (11.7 g, 22 mmol) and the mixture was stirred at 140° C for 3 h. The mixture was cooled to room temp and concentrated. Residue dissolved in CH_2Cl_2 and insoluble solids removed by filtration and discarded. Concentration gave the Intermediate **59** as a brown foam (5.02 g, 47% yield). LCMS (M+H) calcd for $C_{21}H_{28}N_3O_8S$: 482.16; found: 482.11.

Intermediate **60**



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 purified by flash chromatography eluting with 10%-50% EtOAc/hexane to give the Intermediate **60** as a yellow foam (0.477 g, 14% yield). ^{1}H-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 (M+H) calcd for $C_{22}H_{28}N_3O_9S_2$: 542.12; found: 542.03.

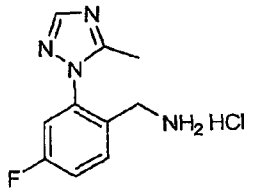
Intermediate **61**



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 Naphthaline (2.56 g, 20 mmol) and THF (20 mL) until the

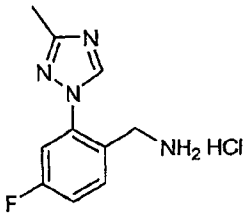
blue color persisted. The resulting mixture stirred an additional 1 h and was quenched with 1N HCl. The aqueous layer was washed with EtOAc and freeze dried. The solids were purified by preparative HPLC (YMC Combiprep ODS-A, 30mm x 50mm, MeOH/H2O/0.1% TFA), to give the Intermediate **61** as a white solid (0.024 g, 10% yield). LCMS (M+H) calcd for $C_{14}H_{20}N_3O_5$: 310.14; found: 310.10.

Intermediate **62**



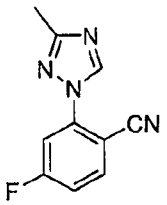
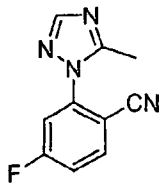
(4-fluoro-2-(5-methyl-1H-1,2,4-triazol-1-yl)phenyl)methanamine hydrochloride: Intermediate **62** was prepared according to procedure for intermediate **35**. LCMS (M+H): 207.2.

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.

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

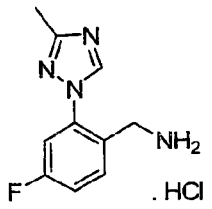



4-Fluoro-2-(3-methyl-1H-1,2,4-triazol-1-yl)benzonitrile and *4-fluoro-2-(5-methyl-1H-1,2,4-triazol-1-yl)benzonitrile.* A solution of 2,4-difluorobenzonitrile (7.07 g, 50.8 mmol) and 3-methyl-1H-1,2,4-triazole (4.22 g, 50.8 mmol) in N,N-dimethylformamide (45 ml) was treated with powdered anhydrous potassium carbonate (10 g) and the resulting mixture was stirred at 22 °C for 18h. The solid 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) 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. ^{1}HNMR 400 MHz ($CDCl_3$) δ (ppm) : 2.54 (3H, s, CH_3), 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 $C_{10}H_7FN_4$: C 59.40, H 3.49, N 27.71; Found: C 59.25, H 3.32, N 27.81.

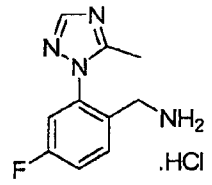
4-fluoro-2-(5-methyl-1H-1,2,4-triazol-1-yl)benzonitrile. white crystals (ethyl acetate – hexane); mp 120 - 121 °C. ^{1}HNMR 400 MHz ($CDCl_3$) δ (ppm) : 2.56 (3H, s, CH_3), 7.30 (1H, dd, J = 2.5 Hz and J = 8.1 Hz, CH), 7.39 (1H, m, CH), 7.91 (1H, dd, J = 5.5 Hz and J = 8.6 Hz, CH), 8.06 (1H, s, CH). Anal. Calcd for $C_{10}H_7FN_4$: C 59.40, H 3.49, N 27.71; Found: C 59.35, H 3.70, N 27.77.

Intermediate **66**



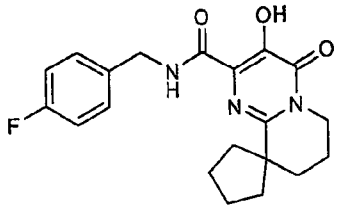
(4-Fluoro-2-(3-methyl-1H-1,2,4-triazol-1-yl)phenyl)methanamine hydrochloride salt. Hydrogenation of 4-fluoro-2-(3-methyl-1H-1,2,4-triazol-1-yl)benzonitrile (0.680 g, 3.36 mmol) gave 0.720 g (88 % yield) of the title hydrochloride salt as a white solid. ^{1}HNMR 400 MHz (DMSO-d_6) δ (ppm) : 2.40 (3H, s, CH_3), 4.02 (2H, m, NCH_2), 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). HRMS (ESI$^+$) calculated for $C_{10}H_{12}FN_4$ [M+H $^+$] : 207.1046 ; found : 207.1047.

Intermediate **67**



(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. ^{1}HNMR 400 MHz (DMSO-d_6) δ (ppm) : 2.42 (3H, s, CH_3), 3.78 (2H, m, NCH_2), 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). HRMS (ESI$^+$) calculated for $C_{10}H_{12}FN_4$ [M+H $^+$] : 207.1046 ; found : 207.1041.

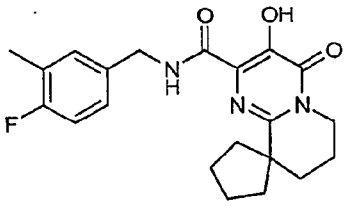
Example 1

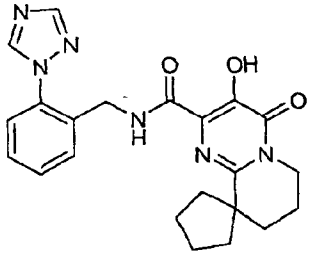
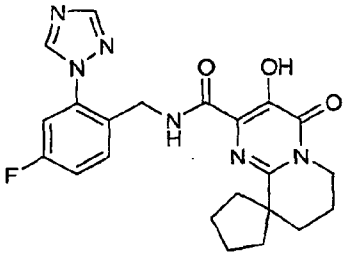
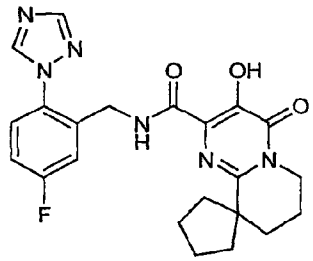


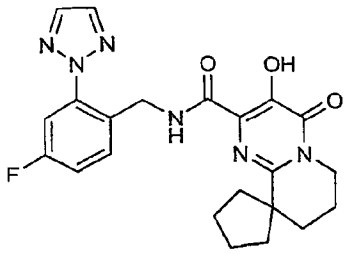
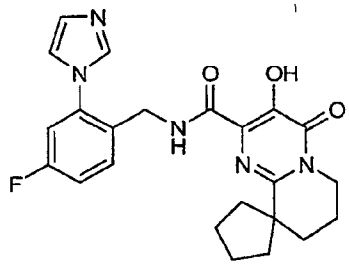
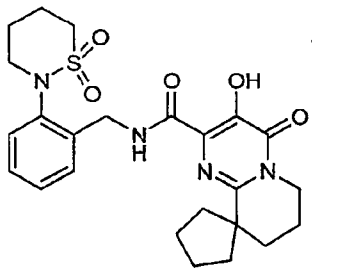
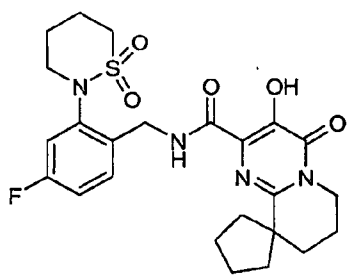
A mixture of ester **3** (0.146 g, .499 mmol), 4-fluorobenzylamine (0.156 g, 1.25 mmol, and triethylamine (0.14 mL, 1 mmol) in 1:1 DMF/EtOH (2 mL) was heated at 110 °C for1.5 h. Then, the reaction mixture was cooled and purified preparative HPLC using MeOH/water containing 0.1F TFA (gradient elution). The fractions containing the product were combined and evaporated to afforded the product as a white solid (0.0955g, 51.5%). ^{1}H NMR (500 MHz, $CDCl_3$) 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 $C_{20}H_{23}FN_3O_3$: 372.1724; found: 371.1714. Anal cald for $C_{20}H_{22}FN_3O_3$: C, 64.67; H, 5.97; N, 11.31. Found: C, 64.58; H, 6.24; N, 11.11.

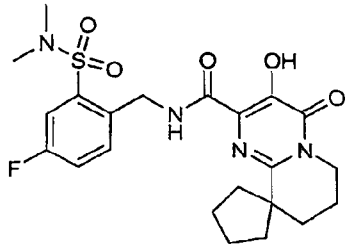
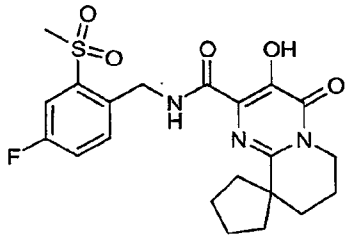
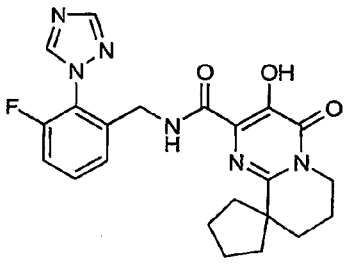
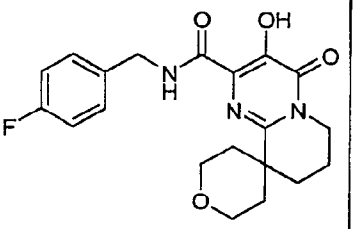
Other examples made by similar methods using amine (2-10 equiv), Et_3N (2-10 equiv.) and appropriate ester in DMF, DMF/EtOH, or other solvent system at 60 °C-140 °C are listed in Table 3.

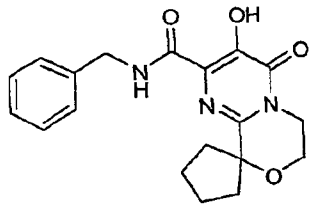
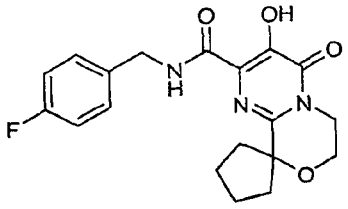
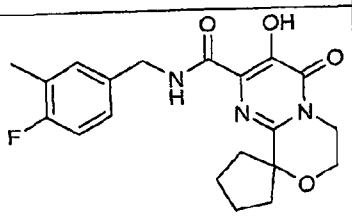
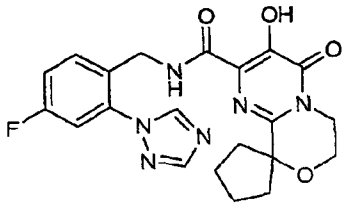
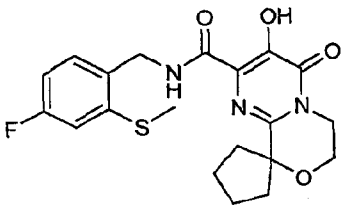
Table 3.

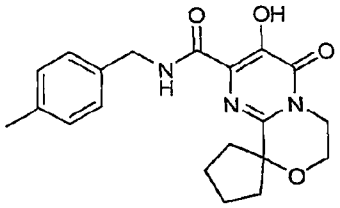
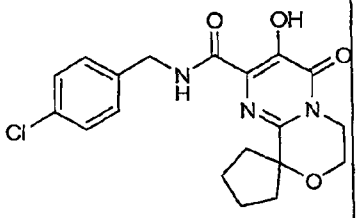
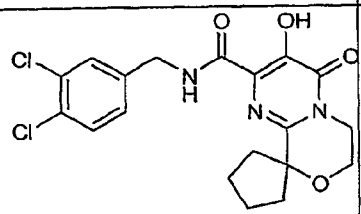
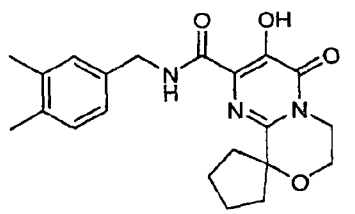
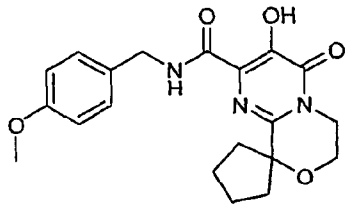
Ex.	Structure	Data
2		Yield: 43%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 11.72 (1H, s), 7.84 (1H, br t), 7.15-7.09 (2H, m), 6.99 (1H, t, J = 8.9 Hz), 4.55 (2H, d, J = 6.1 Hz), 4.01 (2H, t, J = 6.4 Hz), 2.28 (3H, s), 2.17-2.12 (2H, m), 1.99-1.94 (2H, m), 1.83-1.65 (8H, m). HRMS (M+H) calcd for $C_{21}H_{25}FN_3O_3$: 386.188; found: 386.1875. Anal cald for $C_{21}H_{24}FN_3O_3 \bullet 0.03\ H_2O \bullet 0.05\ CH_2Cl_2$: C, 64.79; H, 6.24; N, 10.77; found: C, 64.71; H, 6.31; N, 10.71.

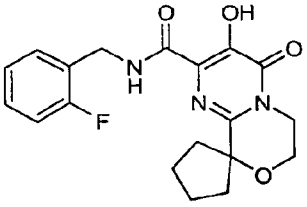
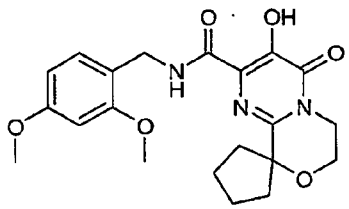
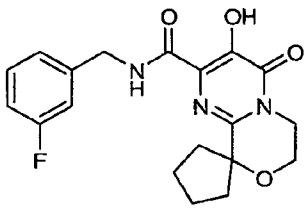
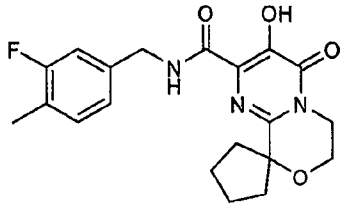
Ex.	Structure	Data
3		Yield: 65%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 11.82 (1H, s), 8.80 (1H, t, J = 6.1 Hz), 8.43 (1H, s), 8.15 (1H, s), 7.73 (1H, dd, J = 7.3, 1.5 Hz), 7.52-7.44 (2H, m), 7.36 (1H, dd, J = 7.6, 1.2 Hz), 4.48 (2H, d, J = 6.7 Hz), 3.99 (2H, t, J = 6.4 Hz), 2.28-2.23 (2H, m), 1.99-1.91 (4H, m), 1.79-1.66 (6H, m). HRMS (M+H) calcd for $C_{22}H_{25}N_6O_3$: 421.1988; found: 421.2001. Anal cald for $C_{22}H_{24}N_6O_3$: 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.H, 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 $C_{22}H_{24}FN_6O_3$: 439.1894; found: 439.1887. Anal cald for $C_{22}H_{23}FN_6O_3$: 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 $C_{22}H_{24}FN_6O_3$: 439.1894; found: 439.1875. Anal cald for $C_{22}H_{23}FN_6O_3$: C, 60.26; H, 5.28; N, 19.16; found: C, 60.14; H, 5.38; N, 19.25.

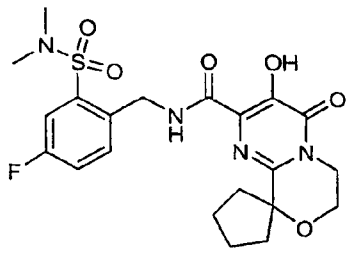
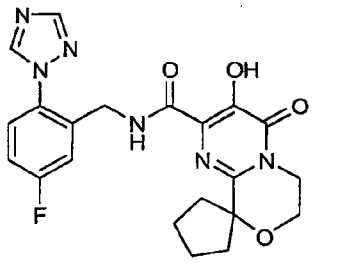
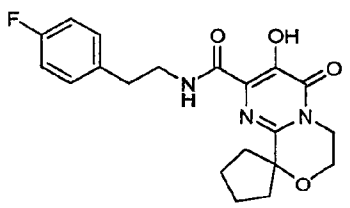
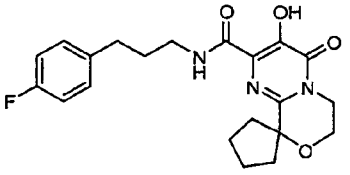
Ex.	Structure	Data
6		Yield:73%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 11.87 (1H, s), 8.91 (1H, t, J = 6.7 Hz), 7.91 (2H, s), 7.69 (1H, dd, J = 8.5, 5.8 Hz), 7.63 (1H, dd, J = 9.3, 2.6 Hz), 7.13 (1H, td, J = 8.2, 2.6 Hz), 4.64 (2H, d, J = 7.0 Hz), 3.99 (2H, t, J = 6.4 Hz), 2.23-2.17 (2H, m), 1.97-1.85 (4H, m), 1.78-1.63 (6H, m). HRMS (M+H) calcd for $C_{22}H_{24}FN_6O_3$: 439.1894; found: 439.1912. Anal cald for $C_{22}H_{23}FN_6O_3$: C, 60.26; H, 5.28; N, 19.16; found: C, 59.97; H, 4.99; N, 19.03.
7		Yield: 63%. ^{1}H 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 $C_{23}H_{25}FN_5O_3$: 438.1941; found: 438.1954. Anal cald for $C_{23}H_{24}FN_5O_3$•0.3 EtOAc: C, 50.92; H, 4.37; N, 10.84; found: C, 50.59; H, 4.14; N, 10.95.
8		Yield: 77%. ^{1}H 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 $C_{24}H_{31}N_4O_5S$: 487.2015; found: 487.2030. Anal cald for $C_{24}H_{30}N_4O_5S$: C, 59.24; H, 6.21; N, 11.51; found: C, 58.94; H, 6.47; N, 11.43.
9		Yield: 70%. ^{1}H 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 $C_{24}H_{30}FN_4O_5S$: 505.1921; found: 505.1942. Anal cald for $C_{24}H_{29}FN_4O_5S$: C, 57.13; H, 5.79; N, 11.10; found: C, 57.01; H, 5.98; N, 11.02.

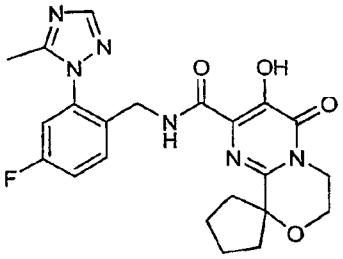
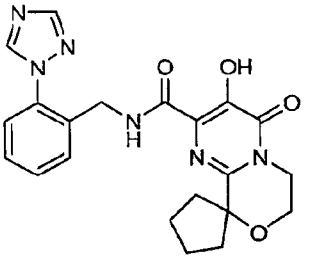
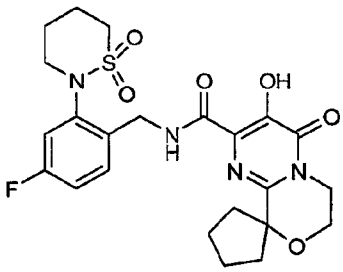
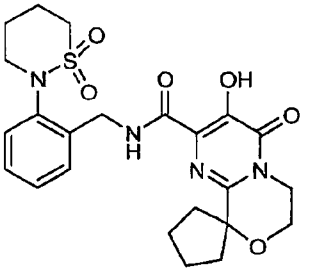
Ex.	Structure	Data
10		Yield: 66%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 11.65 (1H, br s), 8.60 (1H, t, J = 6.7 Hz), 7.69 (1H, dd, J = 8.4, 5.4 Hz), 7.49 (1H, dd, J = 8.4, 2.6 Hz), 7.28-7.24 (1H, m), 4.81 (2H, d, J = 6.7 Hz), 3.98 (2H, t, J = 6.4 Hz), 2.89 (6H, s), 2.22-2.16 (2H, m), 1.96-1.91 (4H, m), 1.76-1.61 (6H, m). HRMS (M+H) calcd for $C_{22}H_{28}FN_4O_5S$: 479.1764; found: 479.1788. Anal cald for $C_{22}H_{27}FN_4O_5S$• 0.8 H_2O: C, 53.60; H, 5.85; N, 11.37; found: C, 53.48; H, 5.50; N, 10.98.
11		Yield: 53%. ^{1}H 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 (M+H) calcd for $C_{21}H_{25}FN_3O_5S$: 450.1499; found: 450.1479. Anal cald for $C_{21}H_{24}FN_3O_5S$: C, 56.11; H, 5.38; N, 9.34; found: C, 55.89; H, 5.39; N, 9.19.
12		Yield: 66%. ^{1}H 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 (M+H) calcd for $C_{22}H_{24}FN_6O_3$: 439.1894; found: 439.1883. Anal cald for $C_{22}H_{23}FN_6O_3$: C, 60.26; H, 5.28; N, 19.16; found: C, 60.06; H, 5.22; N, 19.09.
13		Yield: 59%. ^{1}H 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 (M-H) calcd for $C_{20}H_{21}FN_3O_4$: 386.1516; found: 386.1499. Anal cald for $C_{20}H_{22}FN_3O_4$•0.04 H_2O•0.2 TFA: C, 64.79; H, 6.24; N, 10.77; found: C, 64.71; H, 6.31; N, 10.71.

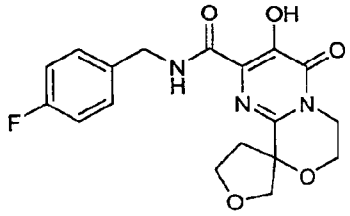
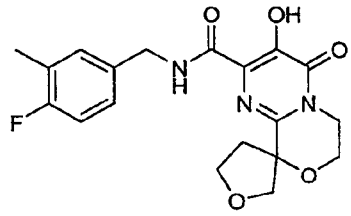
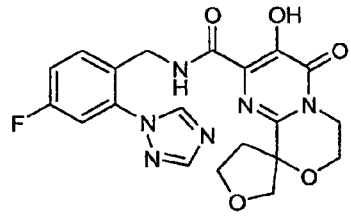
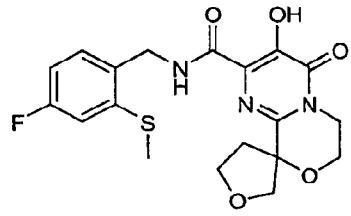
Ex.	Structure	Data
14		Yield: 79%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 12.01 (1H, s), 7.78 (1H, br t), 7.39-7.30 (5H, m), 4.63 (2H, d, J = 6.4 Hz), 4.03-3.96 (4H, m), 2.16-2.04 (4H, m), 1.86-1.79 (4H, m). HRMS (M+H) calcd for $C_{19}H_{22}N_3O_4$: 356.1610; found: 356.1616. Anal cald for $C_{19}H_{21}N_3O_4$: C, 64.21; H, 5.95; N, 11.82; found: C, 63.98; H, 5.81; N, 11.71.
15		Yield: 85%. ^{1}H 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 (M+H) calcd for $C_{19}H_{21}FN_3O_4$: 374.1516; found: 374.1506. Anal cald for $C_{19}H_{20}FN_3O_4 \bullet 0.15$ H_2O: 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%. ^{1}H 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 (M+H) calcd for $C_{20}H_{23}FN_3O_4$: 388.1673; found: 388.1661.
17		Yield: 51%. ^{1}H 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 (M+H) calcd for $C_{21}H_{22}FN_6O_4$: 441.1687; found: 441.1691. Anal cald for $C_{21}H_{21}FN_6O_4$: N, 19.08; F, 4.31; found: N, 19.37; F, 4.56.
18		Yield: 77%. ^{1}H 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 (M+H) calcd for $C_{20}H_{23}FN_3O_4S$: 420.1393; found: 420.1383. Anal cald for $C_{20}H_{22}FN_3O_4S$: 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.

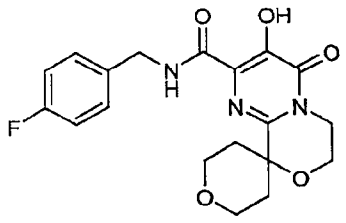
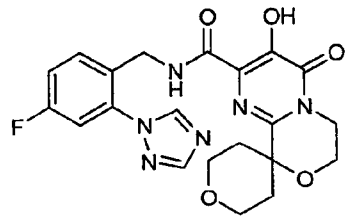
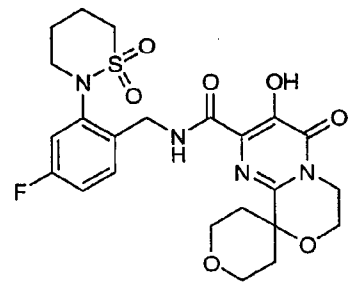
Ex.	Structure	Data
19		Yield: 83%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 12.04 (1H, s) 7.74 (1H, br t), 7.22 (2H, d, J = 7.9 Hz), 7.18 (2H, d, J = 7.9 Hz), 4.58 (2H, d, J = 6.1 Hz), 4.03-3.95 (4H, m), 2.35 (3H, s), 2.15-2.03 (4H, m), 1.87-1.79 (4H, m). HRMS (M+H) calcd for $C_{20}H_{24}N_3O_4$: 370.1767; found: 370.1778. Anal cald for $C_{20}H_{23}N_3O_4$: C, 65.02; H, 6.27; N, 11.37; found: C, 64.93; H, 6.44; N, 11.32.
20		Yield: 75%. ^{1}H 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 $C_{19}H_{21}ClN_3O_4$: 3901221; found: 390-1216. Anal cald for $C_{19}H_{20}ClN_3O_4$: C, 58.54; H, 5.17; N, 10.77; found: C, 58.34; H, 5.24; N, 10.59.
21		Yield: 73%. ^{1}H 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 $C_{19}H_{20}Cl_2N_3O_4$: 424.0831; found: 424.0811.
22		Yield: 85%. ^{1}H 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 $C_{21}H_{26}N_3O_4$: 384.1923; found: 384.1937. Anal cald for $C_{21}H_{25}N_3O_4$: C, 65.78; H, 6.57; N, 10.95; found: C, 65.58; H, 6.58; N, 10.89.
23		Yield: 84%. ^{1}H 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 $C_{20}H_{24}N_3O_5$: 386.1716; found: 386.1697. Anal cald for $C_{20}H_{23}N_3O_5 \bullet 0.11$ CH_2Cl_2: C, 61.19; H, 5.93; N, 10.64; found: C, 60.86; H, 5.98; N,10.55 .

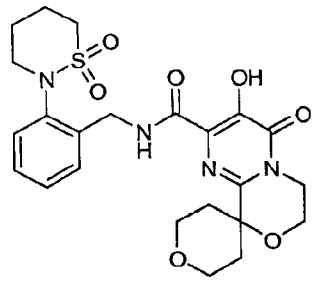
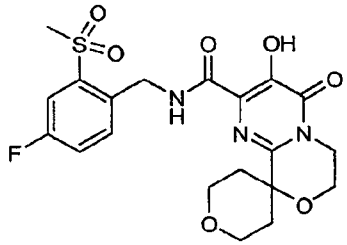
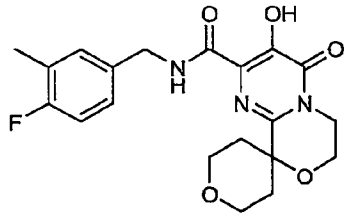
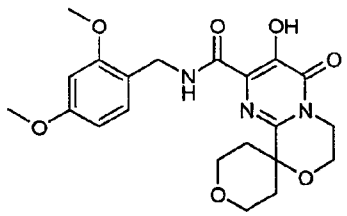
Ex.	Structure	Data
24		Yield: 78%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 11.89 (1H, s), 7.88 (1H, t, J = 5.2 Hz), 7.37 (1H, td, J = 7.6 1.2 Hz), 7.33-7.28 (1H, m), 7.14 (1H, t, J = 7.6 Hz), 7.09 (1H, t, J = 9.3 Hz), 4.66 (2H, d, J = 6.4 Hz), 4.03-3.95 (4H, m), 2.19-2.13 (2H, m), 2.09-2.04 (2H, m), 1.89-1.83 (4H, m). HRMS (M+H) calcd for $C_{19}H_{21}FN_3O_4$: 374.1516; found: 374.1532. Anal cald for $C_{19}H_{20}FN_3O_4$•0.05 Et_2O •0.05 CH_2Cl_2: C, 60.63; H, 5.45; N, 11.02; found: C, 60.58; H, 5.33; N, 11.03.
25		Yield: 88%. ^{1}H 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 (M+H) calcd for $C_{21}H_{26}N_3O_6$: 416.1822; found: 416.1837. Anal cald for $C_{21}H_{25}N_3O_6$: C, 60.71; H, 6.06; N, 10.11; found: C, 60.47; H, 6.10; N, 9.97.
26		Yield: 86%. ^{1}H 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 (M+H) calcd for $C_{19}H_{21}FN_3O_4$: 374.1516; found: 374.1504. Anal cald for $C_{19}H_{20}FN_3O_4$•0.1 CH_2Cl_2: C, 60.07; H, 5.33; N, 11.00; found: C, 60.06; H, 5.39; N, 10.94.
27		Yield: 65%. ^{1}H 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 (M+H) calcd for $C_{20}H_{23}FN_3O_4$: 388.1673; found: 388.1665. Anal cald for $C_{20}H_{22}FN_3O_4$: C, 62.00; H, 5.72; N, 10.84; found: C, 61.73; H, 7.72; N, 10.66.

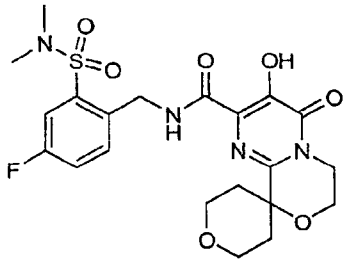
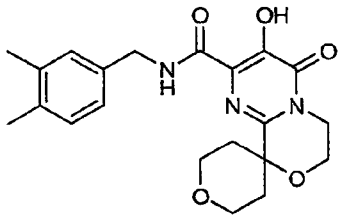
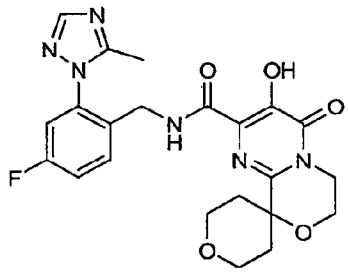
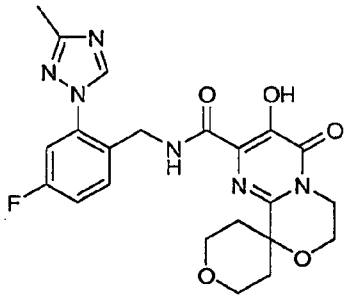
Ex.	Structure	Data
28		Yield: 44%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 11.80 (1H, br s), 8.61 (1H, t, J = 6.7 Hz), 7.68 (1H, dd, J = 8.6, 5.2 Hz), 7.48 (1H, dd, J = 8.4, 2.6 Hz), 7.28-7.24 (1H, m), 4.80 (2H, d, J = 7.0 Hz), 4.00-3.94 (4H, m), 2.90 (6H, s), 2.24-2.18 (2H, m), 2.06-2.00 (2H, m), 1.96-1.80 (4H, m). HRMS (M+H) calcd for $C_{21}H_{26}FN_4O_6S$: 481.1557; found: 481.1561. Anal cald for $C_{21}H_{25}FN_4O_6S$• 0.35 CF_3CO_2H• 0.1 $C_4H_{10}O$: C, 50.29; H, 5.03; N, 10.61; found: C, 50.06; H, 4.70; N, 10.51.
29		Yield: 51%. ^{1}H 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 $C_{21}H_{22}FN_6O_4$: 441.1687; found: 441.1697. Anal cald for $C_{21}H_{21}FN_6O_4$: C, 57.26; H, 4.80; N, 19.08; found: C, 57.27; H, 4.85; N, 19.07.
30		Yield: 87%. ^{1}H 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 $C_{20}H_{23}FN_3O_4$: 388.1673; found: 388.1680. Anal cald for $C_{20}H_{22}FN_3O_4$•0.8 H_2O: C, 60.05; H, 5.90; N, 10.50; found: C, 60.14; H, 5.60; N, 10.51.
31		Yield: 80%. ^{1}H 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 $C_{21}H_{25}FN_3O_4$: 402.1829; found: 402.1840. Anal cald for $C_{21}H_{24}FN_3O_4$: C, 62.83; H, 6.02; N, 10.46; found: C, 62.46; H, 6.26; N, 10.52.

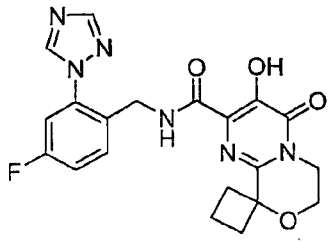
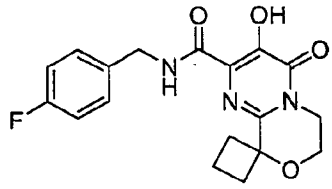
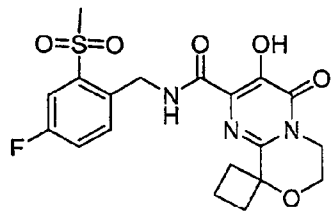
Ex.	Structure	Data
32		Yield: 73%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 12.10 (1H, s), 8.55 (1H, t, J = 6.4 Hz), 8.29 (1H, s), 7.68 (1H, dd, J = 8.6, 6.1 Hz), 7.17 (1H, td, J = 8.6, 2.8 Hz), 7.08 (1H, dd, J = 8.6, 2.8 Hz), 4.47 (2H, d, J = 6.7 Hz), 4.02-4.00 (2H, m), 3.96-3.94 (2H, m), 2.52 (3H, s), 2.23-2.16 (2H, m), 2.09-2.04 (2H, m), 1.88-1.83 (4H, m). HRMS (M+H) calcd for $C_{22}H_{24}FN_6O_4$: 455.1843; found: 455.1850. Anal cald for $C_{22}H_{23}FN_6O_4$: C, 58.14; H, 5.10; N, 18.49; found: C, 58.04; H, 4.98; N, 18.53.
33		Yield: 10%. ^{1}H-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 $[M+H]^+$ calcd for $C_{21}H_{23}N_6O_4$: 423.1781; found: 423.1773.
34		Yield: 59% yield. ^{1}H-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 $[M+H]^+$ calcd for $C_{23}H_{28}N_4O_6FS$: 507.1714; found: 507.1735. Anal cald for $C_{23}H_{27}N_4O_6FS$: 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. ^{1}H-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 $[M+H]^+$ calcd for $C_{23}H_{29}N_4O_6S$: 489.1808; found: 489.1801. Anal cald for $C_{23}H_{28}N_4O_6S$: C, 56.54; H, 5.78; N, 11.47; found: C, 56.63; H, 5.48; N, 11.37.

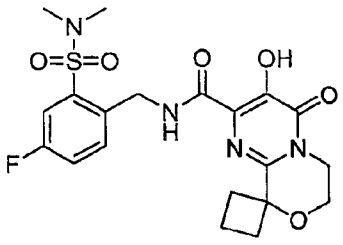
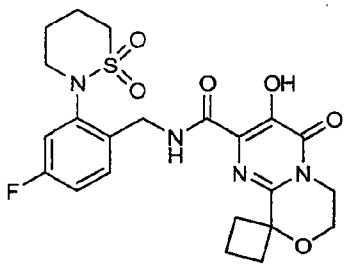
Ex.	Structure	Data
36		Yield: 65%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 12.10 (1H, s), 7.74 (1H, br t), 7.30 (2H, dd, J = 8.5, 5.2 Hz), 7.04 (2H, t, J = 8.5 Hz), 4.62-4.53 (2H, m), 4.14-3.99 (8H, m), 2.51-2.45 (1H, m), 2.36-2.31 (1H, m). HRMS (M+H) calcd for $C_{18}H_{19}FN_3O_5$:; found:. Anal cald for $C_{18}H_{18}FN_3O_5$: 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%. ^{1}H 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 (M+H) calcd for $C_{19}H_{21}FN_3O_5$: 390.1465; found: 390.1451. Anal cald for $C_{19}H_{20}FN_3O_5$: 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%. ^{1}H 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 (M+H) calcd for $C_{20}H_{20}FN_6O_5$: 443.1479; found: 443.1495. Anal cald for $C_{20}H_{19}FN_6O_5$: 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%. ^{1}H 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 (M+H) calcd for $C_{19}H_{21}FN_3O_5S$: 422.1186; found: 422.1165. Anal cald for $C_{19}H_{21}FN_3O_5S$: C, 54.14; H, 4.78; N, 9.97; found: C, 54.22; H, 5.07; N, 9.90.

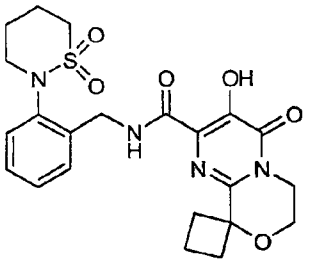
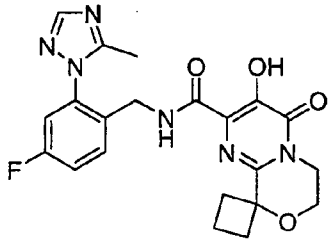
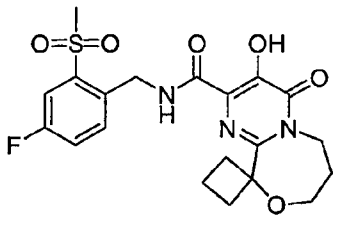
Ex.	Structure	Data
40		Yield: 28%. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 12.07 (1H, s), 7.81 (1H, t, J = 6.0 Hz), 7.32 (2H, dd, J = 8.5, 5.5 Hz), 7.06 (2H, t, J = 8.7 Hz), 4.58 (2H, d, J = 6.4 Hz), 4.05-4.01 (4H, m), 3.84 (2H, dd, J = 11.4, 5.3 Hz), 3.77 (2H, t, J = 11.3 Hz), 2.30 (2H, dt, J = 13.3, 5.2 Hz), 1.79 (2H, d, J = 13.7 Hz).). HRMS [M+H] calcd for $C_{19}H_{21}N_3O_5F$: 390.14653; found: 390.1465. Anal clad for $C_{19}H_{20}N_3O_5F$: 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}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 (M+H) calcd for $C_{21}H_{22}N_6O_5F$: 457.16358; found: 457.1639. Anal cald for $C_{21}H_{21}N_6O_5F$: 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}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 $[M+H]^+$ calcd for $C_{23}H_{28}N_6O_7FS$: 523.1663; found: 523.1666. Anal cald for $C_{23}H_{27}N_6O_7FS\bullet$ 0.5 H_20: 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.

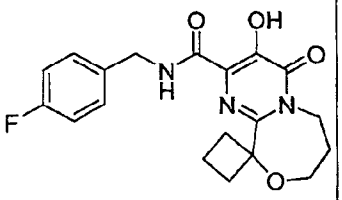
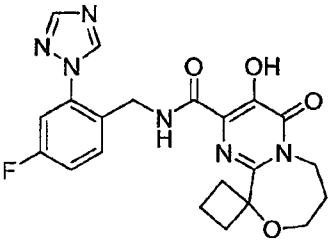
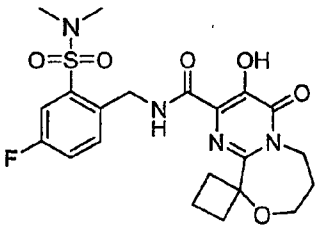
Ex.	Structure	Data
43		Yield: 65%. ^{1}H-NMR (300 MHz, $CDCl_3$/1drop MeOD) δ: 8.28-8.24 (1H, m), 7.46-7.43 (2H, m), 7.35-7.32 (2H, m), 4.89 (1H, dd, J = 14.3, 8.4 Hz), 4.45 (1H, dd, J = 14.3, 4.4 Hz), 3.97 (4H, s), 3.89-3.65 (5H, m), 3.43-3.36 (1H, m), 3.33-3.16 (2H, m), 2.46-2.24 (4H, m), 1.96-1.88 (2H, m), 1.73-1.65 (2H, m). HRMS $[M+H]^+$ calcd for $C_{23}H_{29}N_4O_7S$: 505.1757; found: 505.1761. Anal cald for $C_{23}H_{28}N_4O_7S$: 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}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 H), 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 $[M+H]^+$ calcd for $C_{20}H_{23}N_3O_7SF$: 468.1241; found: 468.1237. Anal cald for $C_{20}H_{22}N_3O_7SF$: 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}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 $[M+H]^+$ calcd for $C_{20}H_{23}N_3O_5F$: 404.1622; found: 404.1615.
46		Yield: 39%. ^{1}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 $[M+H]^+$ calcd for $C_{21}H_{26}N_3O_7$: 432.1771; found: 432.1771. Anal cald for $C_{21}H_{25}N_3O_7$: C, 58.46; H, 5.84; N, 9.74; found: C, 58.22; H, 5.89; N, 9.69.

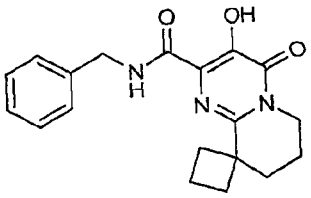
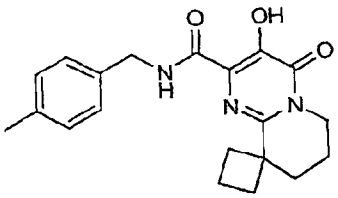
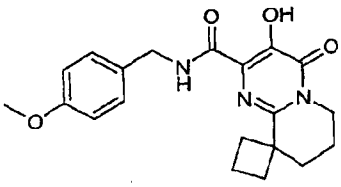
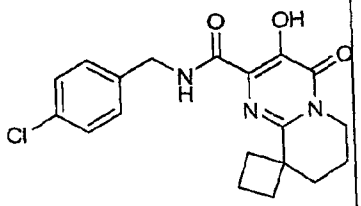
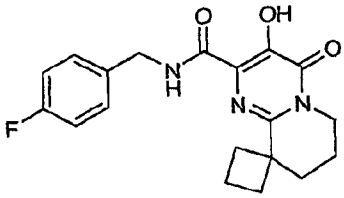
Ex.	Structure	Data
47		Yield: 44%. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 11.91 (1H, s), 8.52 (1H, t, J = 6.6 Hz), 7.63 (1H, dd, J = 8.4, 5.5 Hz), 7.47 (1H, dd, J = 8.4, 2.9 Hz), 7.27-7.22 (1H, m), 4.81 (2H, d, J = 6.9 Hz), 3.98 (4H, s), 3.85-3.70 (4H, m), 2.90 (6H, s), 2.31 (2H, td, J = 13.0, 5.2 Hz), 1.73 (2H, d, J = 13.5 Hz). HRMS $[M+H]^+$ calcd for $C_{21}H_{26}N_4O_7FS$: 497.1506; found: 497.1497. Anal cald for $C_{21}H_{25}N_4O_7FS$: 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}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 $[M+H]^+$ calcd for $C_{21}H_{26}N_3O_5$: 400.1872; found: 400.1869. Anal cald for $C_{21}H_{25}N_3O_5$ C, 63.14; H, 6.30; N, 10.52; found: C, 62.39; H, 6.01; N, 10.23.
49		Yield: 59%. ^{1}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 $[M+H]^+$ calcd for $C_{22}H_{24}N_6O_5F$: 471.1792; found: 471.1786. Anal cald for $C_{22}H_{23}N_6O_5F$: 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}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 $C_{22}H_{24}N_6O_5F$: 471.1792; found: 471.1812. Anal cald for $C_{22}H_{24}N_6O_5F \bullet 0.2$ H_2O: 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.

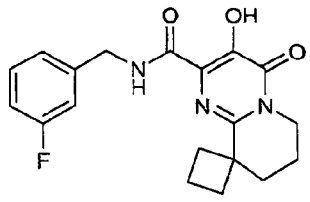
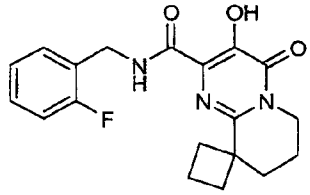
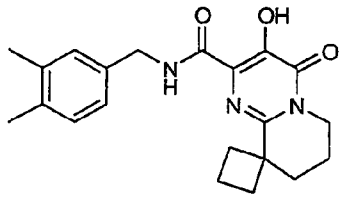
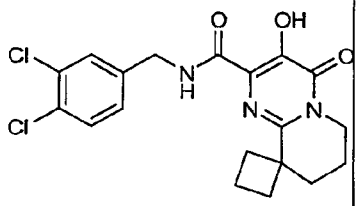
Ex.	Structure	Data
51		Yield: 34%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 12.01 (1H, s), 8.95 (1H, t, J = 6.3 Hz), 8.46 (1H, s), 8.15 (1H, s), 7.73 (1H, dd, J = 8.6, 6.1 Hz), 7.21 (1H, td, J = 8.2, 2.6 Hz), 7.12 (1H, dd, J = 8.6, 2.4 Hz), 4.47 (2H, d, J = 6.7 Hz), 3.96 (4H, s), 2.67-2.75 (2H, m), 2.32-2.40 (2H, m), 2.15-2.24 (1H, m), 2.08 (1H, m). HRMS (M+H) calcd for $C_{20}H_{20}N_6O_4F$: 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, 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 $C_{18}H_{19}N_3O_4F$: 360.1360; found: 360.1350.
53		Yield: 43%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 11.81 (1H, s), 8.68 (1H, t, J = 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 $C_{19}H_{21}FN_3O_6S$: 438.1135, found 438.1149.

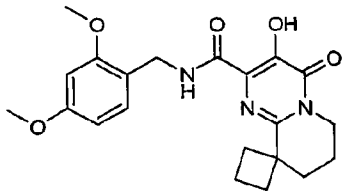
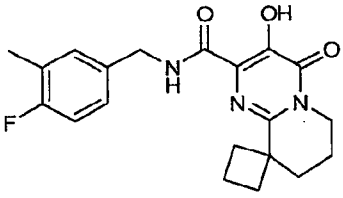
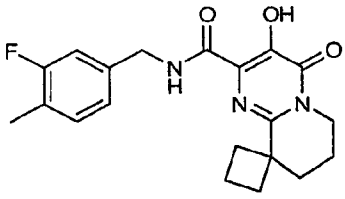
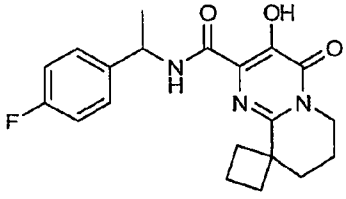
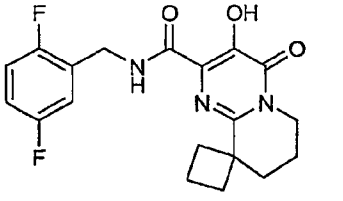
Ex.	Structure	Data
54		Yield: 56%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 11.91 (1H, s), 8.73 (1H, t, J = 6.7 Hz), 7.71 (1H, dd, J = 8.4, 5.3 Hz), 7.49 (1H, dd, J = 8.4, 2.6 Hz), 7.25-7.29 (1H, m), 4.83 (2H, d, J = 7.0 Hz), 3.94 (4H, s), 2.90 (6H, s), 2.64-2.70 (2H, m), 2.28-2.35 (2H, m), 2.12-2.21 (1H, m), 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 (M+H) calcd for $C_{20}H_{24}N_4O_6FS$ 467.1401, found 467.1418. Anal. calcd for $C_{20}H_{23}N_4O_6FS$: 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%. ^{1}H 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 (M+H) calcd for $C_{22}H_{26}N_4O_6FS$ 493.1557; found 493.1549. Anal. calcd for $C_{22}H_{25}N_4O_6FS$: 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.

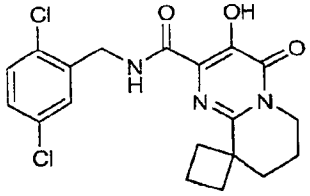
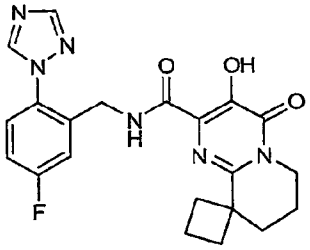
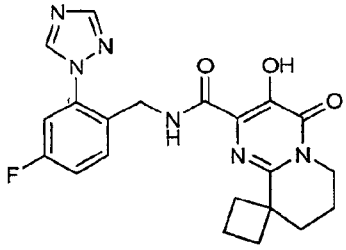
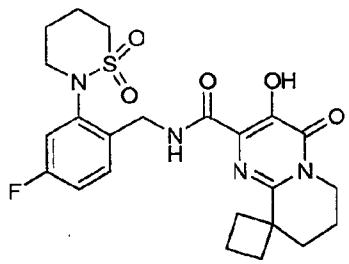
Ex.	Structure	Data
56		Yield: 66%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 12.15-12.29 (1H, br s), 8.32-8.40 (1H, m), 7.47-7.52 (1H, m), 7.42-7.47 (1H, m), 7.33-7.39 (2H, m), 4.99 (1H, dd, J = 14.0, 8.9 Hz), 4.47 (1H, dd, J = 14.3, 3.7 Hz), 3.92-3.98 (4H, m), 3.84-3.92 (1H, m), 3.41-3.47 (1H, m), 3.22-3.28 (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 $C_{22}H_{27}N_4O_6S$ 475.1651; found 475.1665. Anal. calcd for $C_{22}H_{26}N_4O_6S$: 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, J = 8.5, 5.8 Hz), 7.22-7.26 (1H, m), 7.02 (1H, dd, J = 8.4, 2.6 Hz), 4.32 (2H, d, J = 6.7 Hz), 3.94-3.97 (4H, m), 2.72 (2H, ddd, J = 12.7, 9.2, 5.5 Hz), 2.48 (3H, s), 2.36 (2H, ddd, J = 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 $C_{21}H_{22}N_6O_4F$: 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, J = 7.9, 2.8 Hz), 7.71 (1H, dd, J = 8.6, 5.2 Hz), 7.34 (1H, dt, J = 8.0, 2.6 Hz), 4.83 (2H, d, J = 6.7 Hz), 4.36 (2H, br), 3.89 (2H, t, J = 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 $C_{20}H_{23}FN_3O_6S$: 452.1292, found 452.1299.

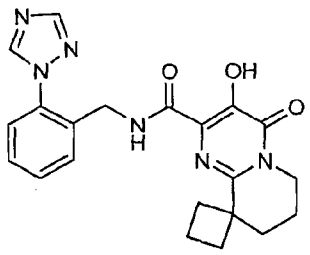
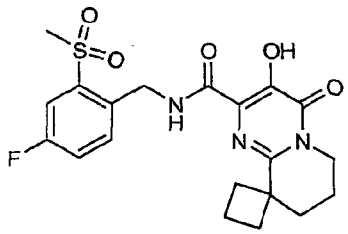
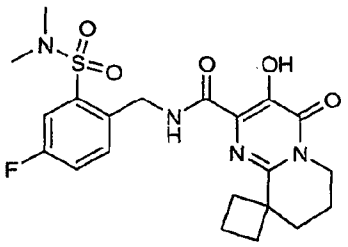
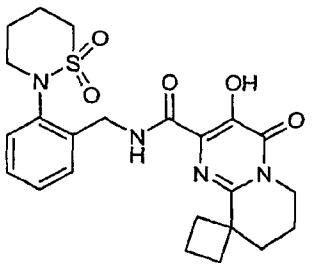
Ex.	Structure	Data
59		Yield: 52%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 12.09 (1H, s), 7.82 (1H, br t), 7.31 (2H, dd, J = 8.1, 5.6 Hz), 7.05 (2H, t, J = 8.5 Hz), 4.59 (2H, d, J = 6.1 Hz), 4.39 (2H, br), 3.92 (2H, t, J = 5.5 Hz), 2.63-2.71 (2H, br), 2.38-2.46 (2H, m), 1.89 (1H, td, J = 10.0, 5.6 Hz), 1.82-1.87 (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 (M+H) calcd for $C_{19}H_{21}FN_3O_4$: 374.1516; found: 374.1515.
60		Yield: 18%. ^{1}H 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 (M+H) calcd for $C_{21}H_{22}FN_6O_4$: 441.1687, found: 441.1695.
61		Yield: 33%. ^{1}H 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 (M+H) calcd for $C_{21}H_{26}FN_4O_6FS$ 481.1557, found 481.1555. Anal. calcd for $C_{21}H_{25}N_4O_6FS$: 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.

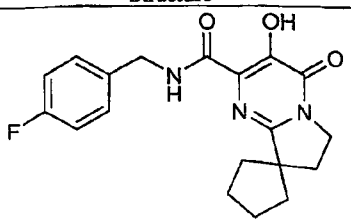
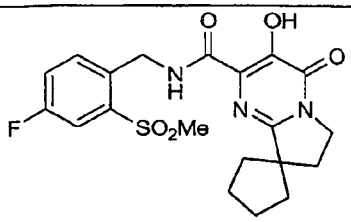
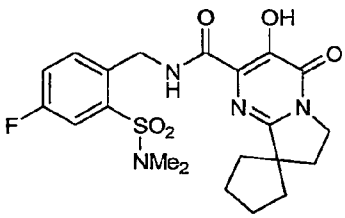
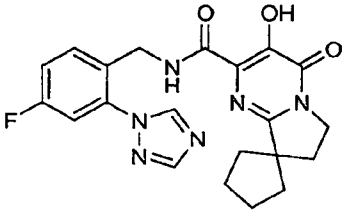
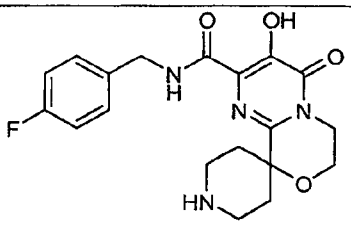
Ex.	Structure	Data
62		Yield: 82%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 11.90 (1H, s), 8.03 (1H, br t), 7.40-7.30 (5H, m), 4.67 (2H, d, J = 6.4 Hz), 3.96 (2H, t, J = 6.4 Hz), 2.63-2.57 (2H, m), 2.07-1.91 (8H, m). HRMS (M+H) calcd for $C_{19}H_{22}N_3O_3$: 340.1661; found: 340.1652. Anal cald for $C_{19}H_{21}N_3O_3$: C, 67.24; H, 6.23; N, 12.38; found: C, 66.85; H, 6.14; N, 12.31.
63		Yield: 78%. ^{1}H 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 $C_{20}H_{24}N_3O_3$: 354.1818; found: 354.1823. Anal cald for $C_{20}H_{23}N_3O_3$: C, 67.97; H, 6.55; N, 11.89; found: C, 67.81; H, 6.84; N, 11.94.
64		Yield: 76%. ^{1}H 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 $C_{20}H_{24}N_3O_4$: 370.1767; found: 370.1780. Anal cald for $C_{20}H_{23}N_3O_4$: C, 65.02; H, 6.27; N, 11.37; found: C, 64.94; H, 6.53; N, 11.46.
65		Yield: 74%. ^{1}H 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 $C_{19}H_{21}ClN_3O_3$: 374.1271; found: 374.1287. Anal cald for $C_{19}H_{20}ClN_3O_3$: C, 61.04; H, 5.39; N, 11.24; found: C, 61.05; H, 5.41; N, 11.10.
66		Yield: 72%. ^{1}H 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 $C_{19}H_{21}FN_3O_3$: 358.1567; found: 358.1551. Anal cald for $C_{19}H_{20}FN_3O_3$: 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%. ^{1}H 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 (M+H) calcd for $C_{19}H_{21}FN_3O_3$: 358.1567; found: 358.1553. Anal cald for $C_{19}H_{20}FN_3O_3$: C, 63.85; H, 5.64; N, 11.75; found: C, 63.86; H, 5.64; N, 11.50.
68		Yield: 75%. ^{1}H 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 (M+H) calcd for $C_{19}H_{21}FN_3O_3$: 358.1567; found: 358.1569. Anal cald for $C_{19}H_{20}FN_3O_3$: C, 63.85; H, 5.64; N, 11.75; found: C, 63.75; H, 5.55; N, 11.70.
69		Yield: 71%. ^{1}H 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 (M+H) calcd for $C_{21}H_{26}N_3O_3$: 368.1974; found: 368.1960. Anal cald for $C_{21}H_{25}N_3O_3$: C, 68.64; H, 6.85; N, 11.43; found: C, 67.93; H, 5.93; N, 11.27.
70		Yield: 91%. ^{1}H 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 (M+H) calcd for $C_{19}H_{20}Cl_2N_3O_3$: 408.0882; found: 408.0871. Anal cald for $C_{19}H_{19}Cl_2N_3O_3$: C, 55.89; H, 4.69; N, 10.29; found: C, 55.65; H, 4.51; N, 10.26.

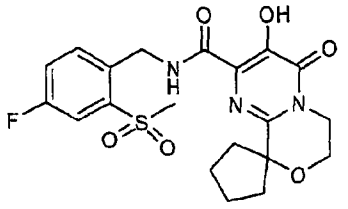
Ex.	Structure	Data
71		Yield: 81%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 11.99 (1H, s), 8.35 (1H, t, J = 5.5 Hz, 7.23 (1H, d, J = 8.2 Hz), 6.49 (1H, d, J = 2.1 Hz), 6.46 (1H, dd, J = 8.2, 2.1 Hz), 4.55 (2H, d, J = 6.4 Hz), 3.94 (2H, t, J = 6.4 Hz), 3.88 (3H, s), 3.80 (3H, s), 2.65-2.59 (2H, m), 2.10-1.89 (8H, m). HRMS (M+H) calcd for $C_{21}H_{26}N_3O_5$: 400.1872; found: 400.1884. Anal cald for $C_{21}H_{25}N_3O_5$: C, 63.14; H, 6.30; N, 10.52; found: C, 62.99; H, 6.46; N, 10.49.
72		Yield: 74%. ^{1}H 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 (M+H) calcd for $C_{20}H_{23}FN_3O_3$: 372.1723; found: 372.1737. Anal cald for $C_{20}H_{22}FN_3O_3$: C, 64.67; H, 5.97; N, 11.31; found: C, 64.73; H, 6.20; N, 11.30.
73		Yield: 73%. ^{1}H 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 (M+H) calcd for $C_{20}H_{23}FN_3O_3$: 372.1723; found: 372.1714. Anal cald for $C_{20}H_{22}FN_3O_3$: C, 64.67; H, 5.97; N, 11.31; found: C, 64.56; H, 6.08; N, 11.41.
74		Yield: 73%. ^{1}H 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 (M+H) calcd for $C_{20}H_{23}FN_3O_3$: 372.1723; found: 372.1708. Anal cald for $C_{20}H_{22}FN_3O_3$: C, 64.67; H, 5.97; N, 11.31; found: C, 63.20; H, 6.22; N, 10.74.
75		Yield: 79%. ^{1}H 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 (M+H) calcd for $C_{19}H_{20}F_2N_3O_3$: 376.1473; found: 376.1483. Anal cald for $C_{19}H_{19}F_2N_3O_3$: 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%. ^{1}H 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 (M+H) calcd for $C_{19}H_{20}Cl_2N_3O_3$: 408.0882; found: 408.0879. Anal cald for $C_{19}H_{19}Cl_2N_3O_3$: C, 55.89; H, 4.69; N, 10.29; found: C, 55.66; H, 4.83; N, 10.27.
77		Yield: 51%. ^{1}H 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 (M+H) calcd for $C_{21}H_{22}FN_6O_3$: 425.1737; found: 425.1735. Anal cald for $C_{21}H_{21}FN_6O_6$: C, 59.42; H, 4.98; N, 19.80; found: C, 59.20; H, 4.88; N, 19.51.
78		Yield: 59%. ^{1}H 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 (M+H) calcd for $C_{21}H_{22}FN_6O_3$: 425.1737; found: 425.1727. Anal cald for $C_{21}H_{21}FN_6O_6$: C, 59.42; H, 4.98; N, 19.80; found: C, 59.35; H, 4.69; N, 19.85.
79		Yield: 53%. ^{1}H 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 (M+H) calcd for $C_{23}H_{28}FN_4O_5S$: 491.1764; found: 491.1776. Anal cald for $C_{23}H_{27}FN_4O_5S$: 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 $C_{21}H_{23}N_6O_3$: 407.1832; found: 407.1833. Anal cald for $C_{21}H_{22}N_6O_3$: 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 $C_{20}H_{23}FN_3O_5S$: 436.1342; found: 436.1325. Anal cald for $C_{20}H_{22}FN_3O_5S$: 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 $C_{21}H_{26}FN_4O_5S$: 465.1608; found: 465.1593. Anal cald for $C_{21}H_{25}FN_4O_5S$•0.44 CF_3CO_2H: 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 $C_{23}H_{29}N_4O_5S$: 473.1859; found: 473.1866. Anal cald for $C_{23}H_{28}N_4O_5S$•0.12 C_2H_5OH•0.3 H_2O: C, 57.73; H, 6.11; N, 11.59; found: C, 57.48; H, 5.67; N, 11.47.

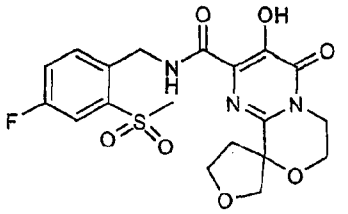
Ex.	Structure	Data
84		Yield = 47%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.65-2.02 (8 H, m), 2.07 (2 H, t, J = 7 Hz), 4.03 (2 H, t, J = 7 Hz), 4.55 (2 H, d, J=6.2 Hz), 7.02 (2 H, t, J=8.6 Hz), 7.29 (2 H, dd, J = 8.6, 5.3 Hz), 7.90 (1 H, brs), 12.09 (1 H, s). HRMS (M+H)calcd for $C_{19}H_{21}FN_3O_3$: 358.1567; found: 358.1578.
85		Yield = 54%. ^{1}H 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 H), 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 $C_{20}H_{23}FN_3O_5S$: 436.1342; found 436.1341.
86		Yield = 15%. ^{1}H 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, = 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 $C_{21}H_{26}FN_4O_5S$: 465.1608; found 465.1626.
87		Yield = 13%. ^{1}H 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 $C_{21}H_{22}FN_6O_3$: 425.1737; found 425.1741.
88		Yield: 27%. ^{1}H-NMR (300 MHz, $CDCl_3$/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 $C_{19}H_{22}N_4O_4F$: 389.1625; found: 389.1610.

Example 89



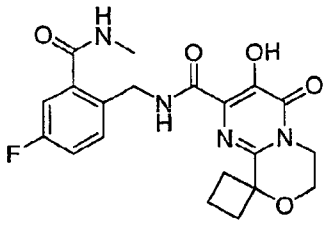
A mixture of example **18** (52 mg, 0.124 mmol) and mCPBA (64.2 mg, 0.372 mmol) in CH_2Cl_2 was stirred at room temperature for 4 h. Then, concentrated and purified by preparative HPLC to afford example **89** (26.2 mg, 47%) as a purple solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 11.69 (1H, s), 8.54 (1H, 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 $C_{20}H_{23}FN_3O_6S$: 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. ^{1}H NMR (500 MHz, $CDCl_3$) 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 $C_{19}H_{21}FN_3O_7S$: 454.1084; found: 454.1096.

Example 91

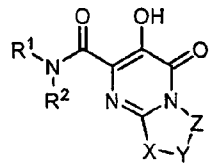


A solution of intermediate **45** (0.096 g, 0.190 mmol) in dichloromethane (5 mL) and trifluoroacetic acid (5 mL) was stirred for 2 hours, and then solvent was removed in-vacuo to give a yellow oil. The oil was triturated with a minimal volume of 95% ethanol, and solids were collected by filtration to give **91** (0.056 g, 71%) as a white solid after vacuum pump drying: ^{1}H NMR (500 MHz, DMSO-D_6) 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), 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). ^{13}C NMR (126 MHz, DMSO-D_6) 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, 40.33, 33.95, 26.06, 13.08. HRMS (M+H) calc'd for $C_{20}H_{22}N_4O_5F$: 417.1574; found: 417.1589.

CLAIMS

I claim:

1. A compound of Formula I



I

wherein:

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

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

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;

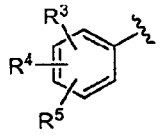
R^4 is hydrogen, halo, hydroxy, cyano, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}haloalkyl, or C_{1-6}haloalkoxy;

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

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^1 is ;

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

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.

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 $CH_2CH_2CH_2$, $CH_2CH_2CH_2CH_2$, $CH_2CH_2CH_2CH_2CH_2$, $CH_2CH_2CH_2CH_2CH_2CH_2$, $CH_2OCH_2CH_2$, $CH_2CH_2OCH_2CH_2$, $CH_2N(R^6)CH_2CH_2$, or $CH_2CH_2N(R^6)CH_2CH_2$.

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;

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;

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;

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;

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;

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;

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;

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;

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;

N-[(4-fluorophenyl)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;

N-[(4-fluoro-3-methylphenyl)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;

N-[[4-fluoro-2-(1H-1,2,4-triazol-1-yl)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;

N-[[4-fluoro-2-(methylthio)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;

N-[(4-fluorophenyl)methyl]-2,3,5,6,6',7'-hexahydro-3'-hydroxy-4'-oxo-spiro[4H-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]-2,3,5,6,6',7'-hexahydro-3'-hydroxy-4'-oxo-spiro[4H-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;

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;

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;

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;

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;

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;

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;

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;

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;

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;

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-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;

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-(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; and

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.

5. A compound of claim 1 where X-Y-Z is $C(R^8)(R^9)OCH_2$, $C(R^8)(R^9)OCH_2CH_2$, or $C(R^8)(R^9)OCH_2CH_2CH_2$.

6. A compound of claim 5 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 $CH_2CH_2N(R^6)CH_2CH_2$.

7. A compound of claim 5 selected from the group consisting of

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;

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;

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-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;

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;

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-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;

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'-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;

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;

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;

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;

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;

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;

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;

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

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;

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-(1H-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-[[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;

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;

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;

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;

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;

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;

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;

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;

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;

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-*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;

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'-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(2H),9'(4'H)-pyrimido[2,1-c][1,4]oxazine]-2'-carboxamide; and

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;

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. Use of a compound of Claim 1, in the manufacture of a medicament for inhibiting HIV viral DNA integration into human DNA.

11. Use of a compound of Claim 1, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of medicament for treating HIV infection.

12. Use of claim 11, wherein said medicament is administrable with one or more other HIV treatment agents selected from the group consisting of HIV protease inhibitors, HIV nucleoside reverse transcriptase inhibitors, HIV non-nucleoside reverse transcriptase inhibitors, HIV-entry inhibitors, HIV integrase inhibitors, immunomodulators, or a combination thereof.

13. A compound of any one of claims 1 to 7, substantially as herein described with reference to and as illustrated in any of the examples.

14. A composition of claim 8, substantially as herein described with reference to and as illustrated in any of the examples.

15. A method of claim 9, substantially as herein described with reference to and as illustrated in any of the examples.

16. Use of any one of claims 10 to 12, substantially as herein described with reference to and as illustrated in any of the examples.