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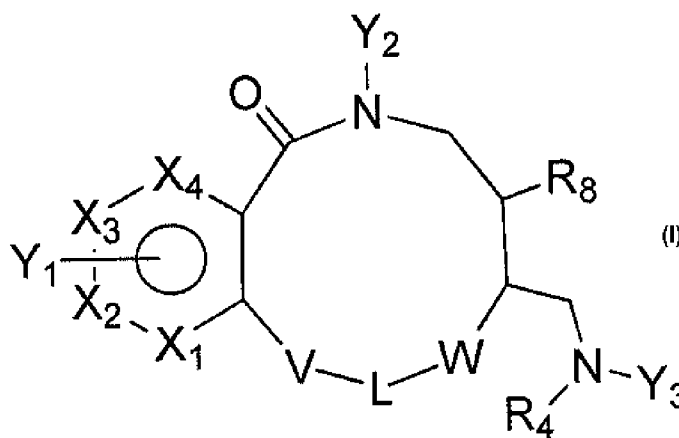
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(54) Title: MACROLACTAM COMPOUNDS AND METHODS FOR THE TREATMENT OF MALARIA



(57) Abstract: The present invention relates to a macrolactam compound, and methods for treating a subject with malaria using the macrolactam compound, represented by the following structural formula (I), wherein the values and preferred values of the variables are defined herein.



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- 1 -

MACROLACTAM COMPOUNDS AND METHODS FOR THE TREATMENT OF MALARIA

RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No.
5 61/618,501, filed on March 30, 2012, and U.S. Provisional Application No.
61/476,105, filed on April 15, 2011. The entire teachings of the above applications
are incorporated herein by reference.

GOVERNMENT SUPPORT

The invention was supported, in whole or in part, by grant US4-
10 IUS4HG005032-01 from the NIH Molecular Libraries Probe Center Network. The
Government has certain rights in the invention.

BACKGROUND OF THE INVENTION

Malaria is a vector-borne infectious disease caused by protozoan parasites
and is widespread in tropical and subtropical regions, including parts of the
15 Americas, Asia and Africa. Of the five *Plasmodium* parasite species that can infect
humans (*P. falciparum*, *P. vivax*, *P. ovale*, *P. malariae* and *P. knowlesi*), the most
serious forms of the disease are caused by *P. falciparum* and *P. vivax*. Of the
approximately 515 million people infected yearly, between one and three million
people, the majority of whom are young children in Sub-Saharan Africa, die from
20 the disease. The current armament of approved anti-malarial drugs, such as
chloroquine, atovaquone, pyrimethamine, and sulfadoxine, is limited to only a few
targets within the human malaria parasite, and growing widespread resistance to
current drugs is prompting the development of new antimalarial agents that have
new biological targets.

SUMMARY OF THE INVENTION

It has now been found that a novel class of compounds based on a macrolactam scaffold (referred to herein as “macrolactam compounds”) has efficacy in the treatment of malaria. Representative compounds disclosed herein exhibit
5 potent anti-malaria activity *in vitro* and *in vivo* and likely act via a mechanism that has not been utilized in malaria drug development.

Accordingly, one embodiment of the present invention is a method of treating a subject with malaria, comprising administering to the subject an effective
10 amount of a macrolactam compound of the invention, or a pharmaceutically acceptable salt thereof, or a composition comprising a macrolactam compound of the invention, or a pharmaceutically acceptable salt thereof.

Another embodiment of the invention is a macrolactam compound described herein, or a pharmaceutically acceptable salt thereof.

Another embodiment of the invention is a composition (*e.g.*, pharmaceutical
15 compositions) comprising a macrolactam compound described herein, or a pharmaceutically acceptable salt thereof.

Another embodiment of the invention is a method of preparing a macrolactam compound described herein, or a pharmaceutically acceptable salt thereof.

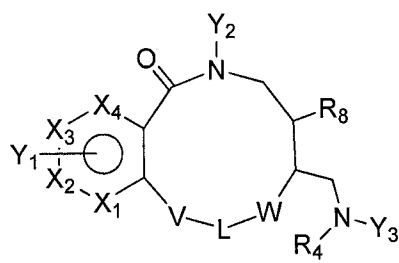
20 Another embodiment of the invention is the use of a macrolactam compound described herein, or a pharmaceutically acceptable salt thereof, for treating malaria in a subject.

Another embodiment of the invention is the use of a macrolactam compound described herein, or a pharmaceutically acceptable salt thereof, for the manufacture
25 of a medicament for treating malaria in a subject.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to a macrolactam compound represented by the following structural formula:

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(I), or a pharmaceutically acceptable salt thereof.

Values and alternative values for the variables in Structural Formula I are defined as follows:

L is C₁-C₁₀ alkylene, C₁-C₁₀ alkenylene, or C₁-C₁₀ alkynylene. L is C₁-C₅ alkylene, C₁-C₅ alkenylene, or C₁-C₅ alkynylene. L is C₂-C₅ alkylene or C₂-C₅ alkenylene. Alternatively, L is C₁-C₅ alkylene or C₁-C₅ alkenylene.

L is optionally substituted with 1 to 3 groups represented by R₅. L is optionally substituted with 1 group represented by R₅. L is substituted with methyl. Alternatively, L is unsubstituted.

Each of X₁, X₃, and X₄ is independently S, O, N, NH or CH. Each of X₁, X₃, and X₄ is independently S, N, NH or CH. Each of X₁, X₃, and X₄ is independently N, NH or CH. Each of X₁, X₃, and X₄ is independently N or CH.

X₂, if present, is S, O, N, NH or CH. X₂ is S, O, N, NH or CH.

Alternatively, X₂ is absent. X₂, if present, is S, N, NH or CH. X₂, if present, is N, NH or CH. X₂, if present, is N or CH.

Y₁, if present, is bonded to any one of X₁, X₃ and X₄ or X₂, if present. Y₁ is present and is bonded to any one of X₁, X₃ and X₄ or X₂, if present. Y₁ is present and is bonded to X₃. Alternatively, Y₁ is present, and is bonded to X₂. Y₁, if present, is bonded to X₁ or X₃ or X₂, if present. Y₁, if present, is bonded to X₃ or X₂, if present. Y₁ is present and is bonded to X₁.

The X₁, X₃ and X₄ or X₂, if present, to which Y₁ is bonded is C or N. The X₁, X₃ and X₄ or X₂, if present, to which Y₁ is bonded is C. Alternatively, the X₁, X₃ and X₄ or X₂, if present, to which Y₁ is bonded is N.

Y₁ is R₁, R₁-(C₁-C₃)alkylene, R₁-(C₂-C₃)alkenylene, R₁-(C₂-C₃)alkynylene, R₁-NR₆⁻, R₁-O-, R₁-S-, R₁-C(O)-, R₁-C(S)-, R₁-SO₂-, R₁-S(O)-, R₁-C(O)NR₆⁻, R₁-NR₆C(O)-, R₁-C(O)O-, R₁-OC(O)-, R₁-C(S)NR₆⁻, R₁-NR₆C(S)-, R₁-C(S)O-, R₁-OC(S)-, R₁-NR₆C(O)NR₆⁻, R₁-NR₆C(S)NR₆⁻, R₁-SO₂NR₆⁻, R₁-NR₆SO₂-, or

- R₁-NR₆C(O)O-, wherein the R₁-(C₁-C₃)alkylene, R₁-(C₂-C₃)alkenylene, or R₁-(C₂-C₃)alkynylene. Y₁ is R₁, R₁-(C₁-C₃)alkylene, R₁-NR₆-, R₁-C(O)NR₆-, R₁-C(O)O-, or R₁-SO₂NR₆-. Y₁ is R₁, R₁-CH₂-, R₁-NR₆-, R₁-C(O)NR₆-, R₁-C(O)O-, R₁-NR₆C(O)NR₆-, or R₁-SO₂NR₆-. Y₁ is R₁, R₁-NH-, R₁-C(O)NH-,
- 5 R₁-NHC(O)NH-, or R₁-SO₂NH-. Y₁ is R₁-NHC(O)NH-. Y₁ is not R₁-NHC(O)NH- when R₁ is unsubstituted phenyl.

Y₁ is optionally substituted with one to three groups selected from R₅.

- R₁ is hydrogen, halogen, -N(R₆)₂, -CN, (C₁-C₆)alkyl, halo(C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)alkoxy(C₁-C₆)alkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl,
- 10 cycloalkyl(C₁-C₃)alkyl, aryl(C₁-C₃)alkyl, heteroaryl(C₁-C₃)alkyl, heterocyclyl(C₁-C₃)alkyl, spiro cycloalkyl, or spiro heterocyclyl. R₁ is hydrogen, halogen, -N(R₆)₂, -CN, (C₁-C₆)alkyl, halo(C₁-C₆)alkyl, cycloalkyl, aryl or heteroaryl. R₁ is hydrogen, fluoro, -CF₃, NH₂, -CN, (C₁-C₃)alkyl, phenyl, isoxazolyl, benzoxazolyl, imidazolyl, pyridine, or thiophene.

- 15 R₁ is optionally substituted with one to three groups represented by R₅.

- Y₂ is R_{2a}-(C₁-C₃)alkylene-, R_{2a}-C(O)-, R_{2a}-SO₂-, R_{2a}-S(O)-, R_{2a}-C(O)NR₆-, R_{2a}-SO₂NR₆-, R_{2a}-R₆C(O)-, or R_{2a}-NR₆SO₂-, wherein the R_{2a}-(C₁-C₃)alkylene is optionally substituted with one to three groups selected from R₅; or Y₂ is R_{2b}-. Y₂ is R_{2b} or R_{2a}-(C₁-C₂)alkylene-. Y₂ is R_{2a}-CH₂CH₂CH(CH₃)- or Y₂ is R_{2b}-. Y₂ is R_{2b}-. Y₂ is not -CH(CH₃)CH₂OH.
- 20

- R_{2a} is hydrogen, halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)alkoxy(C₁-C₆)alkyl, cycloalkyl, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclyl, cycloalkyl(C₁-C₃)alkyl, aryl(C₁-C₃)alkyl, heteroaryl(C₁-C₃)alkyl, heterocyclyl(C₁-C₃)alkyl, spiro cycloalkyl, or spiro heterocyclyl. R_{2a} is (C₁-C₆)alkoxy, aryloxy, or
- 25 heteroaryloxy. R_{2a} is (C₁-C₆)alkyl, (C₁-C₆)alkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, or heteroaryl(C₁-C₃)alkyl.

- R_{2a} is optionally substituted with one to three groups represented by R₅ or further selected from -N₃, aryloxy, aroyl, benzoate, tert-butyldimethylsiloxy, cycloalkoxy, heterocycliloxy, or heteroaryl. R_{2a} is optionally substituted with one
- 30 to three groups represented by R₅ or further selected from -N₃, pyridinoxy, benzoxy,

p-methoxybenzoxo, benzoate, heterocycloxy, tert-butyldimethylsiloxy, or heteroaryl. R_{2a} is optionally substituted with one to three groups represented by R_5 .

R_{2b} is hydrogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy (C_1-C_6) alkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, cycloalkyl (C_1-C_3) alkyl, aryl (C_1-C_3) alkyl, heteroaryl (C_1-C_3) alkyl, heterocyclyl (C_1-C_3) alkyl, spiro cycloalkyl, or spiro heterocyclyl. R_{2b} is $CH_3CH_2CH(CH_3)-$. R_{2b} is hydrogen, (C_1-C_6) alkyl, aryl, or heteroaryl. R_{2b} is 1-methylethyl. When R_{2b} is 1-methylethyl, R_{2b} is not substituted with hydroxy.

R_{2b} is optionally substituted with one to three groups represented by R_5 or further selected from $-N_3$, aryloxy, aroyl, benzoate, tert-butyldimethylsiloxy, cycloalkoxy, heterocycloxy, or heteroaryl. R_{2b} is optionally substituted with one to three groups represented by R_5 or further selected from $-N_3$, pyridinoxy, benzoxo, p-methoxybenzoxo, benzoate, heterocycloxy, tert-butyldimethylsiloxy, or heteroaryl. R_{2b} is optionally substituted with one group represented by R_5 or further selected from benzoate, tert-butyldimethylsiloxy, or heterocycloxy. R_{2b} is optionally substituted with p-methoxybenzoxo, (C_1-C_4) alkoxy, hydroxy, or dimethylamino.

Y_3 is R_3- , $R_3-(C_1-C_3)$ alkylene, $R_3-C(O)O-$, $R_3-OC(O)-$, $R_3-C(O)-$, R_3-SO_2- , R_3-SO- , $R_3-C(O)NR_6-$, R_3-NR_6CO- , $R_3-SO_2NR_6$, or $R_3-NR_6SO_2-$, wherein the $R_3-(C_1-C_3)$ alkylene is optionally substituted with R_5 . Y_3 is R_3 , R_3-CH_2- , $R_3-C(O)O-$, $R_3-C(O)-$, R_3-SO_2- , or $R_3-C(O)NR_6-$. Y_3 is R_3- , $-CH_2-$, $-C(O)O-$, $-C(O)-$, $-SO_2-$, or $-C(O)NR_6-$. Y_3 is R_3SO_2- .

R_3 is hydrogen, halogen, (C_1-C_6) alkyl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, (C_1-C_6) alkoxy, (C_1-C_6) alkoxy (C_1-C_6) alkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, cycloalkyl (C_1-C_3) alkyl, aryl (C_1-C_3) alkyl, heteroaryl (C_1-C_3) alkyl, heterocyclyl (C_1-C_3) alkyl, spiro cycloalkyl, or spiro heterocycyl. R_3 is hydrogen, (C_1-C_6) alkyl, (C_1-C_6) alkenyl, (C_1-C_6) alkoxy, (C_1-C_6) alkoxy (C_1-C_6) alkyl, (C_3-C_7) cycloalkyl, phenyl, or heteroaryl. R_3 is phenyl.

R_3 is optionally substituted with one to three groups represented by R_5 . R_3 is optionally substituted with fluoro, chloro, methyl, methoxy, trifluoromethyl, or carboxy.

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R₄ is hydrogen or (C₁-C₆)alkyl. R₄ is hydrogen, methyl, ethyl, propyl, isopropyl, or tert-butyl. R₄ is hydrogen or methyl. R₄ is hydrogen. Alternatively, R₄ is methyl.

R₄ is optionally substituted with one to three groups represented by R₅.

5 Alternatively, R₄ is unsubstituted.

R₄ and R₃, taken together, form a 5- to 7-membered heterocyclyl, heteroaryl, or spiro heterocyclyl, wherein each ring of the spiro heterocyclyl independently includes 3 to 7 atoms including Y₃ and the nitrogen atom to which R₄ is attached and is optionally substituted with 1 to 3 groups represented by R₅. R₄ and R₃, taken
10 together, form a 5- to 7-membered heterocyclyl. R₄ and R₃, taken together, form a 6-membered heterocyclyl.

V and W are each independently selected from -NR₆-, -C(R₆)₂-, -O-, -S-, -S(O)-, and -S(O)₂-. V and W are each independently selected from -NR₆- and -O-. V is selected from -NR₆- and -O- and W is -O-. V and W are each -O-.

15 Each R₅ is independently selected from halogen, nitro, cyano, isocyano, hydroxy, (C₁-C₄)alkyl, (C₃-C₆)cycloalkyl, halo(C₁-C₄)alkyl, hydroxy(C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, H(CH₂CH₂O)_m-, H(CH₂OCH₂O)_m-, H(CH₂O)_m-, H(CH₂OCH₂CH₂O)_n-, H(CH₂CH₂OCH₂O)_n-, H(OCH₂OCH₂CH₂)_n-, H(OCH₂CH₂OCH₂)_n-, H(CH₂OCH₂CH₂OCH₂O)_n-, H(CH₂OCH₂)-, halo(C₁-
20 C₄)alkoxy, aryl, aryloxy, N(R₆)₂, -CO₂R₆, -OCOR₆, -NR₆CO₂R₆, -NR₆CO₂NR₆, -SO₂R₆, -SOR₆, -SO₃R₆, -NR₆SO₂R₆, -SO₂N(R₆)₂, morpholino, piperadyl, and piperazyl. Each R₅ is independently selected from (C₁-C₄)alkoxy, H(CH₂CH₂O)_m-, H(CH₂OCH₂O)_m-, H(CH₂O)_m-, H(CH₂OCH₂CH₂O)_n-, H(CH₂CH₂OCH₂O)_n-, H(OCH₂OCH₂CH₂)_n-, H(OCH₂CH₂OCH₂)_n-, H(CH₂OCH₂CH₂OCH₂O)_n-,
25 H(CH₂OCH₂)-, aryl and aryloxy. Each R₅ is independently selected from fluoro, chloro, cyano, hydroxy, (C₁-C₄)alkyl, halo(C₁-C₄)alkyl, hydroxy(C₁-C₄)alkyl, (C₁-C₄)alkoxy, H(CH₂OCH₂CH₂OCH₂O)_n-, H(CH₂OCH₂)-, H(CH₂OCH₂O)-, -NH₂, -N(CH₃)₂, -NHCH₃, -CO₂R₆, -NR₆CO₂R₆, -NR₆CO₂NR₆, -SO₂R₆, -NR₆SO₂R₆, and -SO₂N(R₆)₂.

30 Each R₆ is independently selected from hydrogen and (C₁-C₄)alkyl. Each R₆ is independently selected from hydrogen and methyl. R₆ is hydrogen.

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R₈ is hydrogen or (C₁-C₄)alkyl. R₈ is hydrogen or methyl. R₈ is hydrogen. Alternatively, R₈ is methyl.

m is 1, 2, 3, 4, 5, or 6. m is 1, 2, or 3. m is 1.

n is 1, 2, or 3. n is 1 or 2. n is 1.

5 A first embodiment is a compound represented by Structural Formula I, or a pharmaceutically acceptable salt thereof, wherein:

L is C₁-C₁₀ alkylene, C₁-C₁₀ alkenylene, or C₁-C₁₀ alkynylene and is optionally substituted with 1 to 3 groups represented by R₅;

each of X₁, X₃, and X₄ is independently S, O, N, NH or CH and X₂, if
10 present, is S, O, N, NH or CH, wherein Y₁, if present, is bonded to any one of X₁, X₃ and X₄ or X₂, if present, and wherein the X₁, X₃ and X₄ or X₂, if present, to which Y₁ is bonded is C or N;

Y₁ is R₁, R₁-(C₁-C₃)alkylene, R₁-(C₂-C₃)alkenylene, R₁-(C₂-C₃)alkynylene, R₁-NR₆-, R₁-O-, R₁-S-, R₁-C(O)-, R₁-C(S)-, R₁-SO₂-, R₁-S(O)-, R₁-
15 C(O)NR₆-, R₁-NR₆C(O)-, R₁-C(O)O-, R₁-OC(O)-, R₁-C(S)NR₆-, R₁-NR₆C(S)-, R₁-C(S)O-, R₁-OC(S)-, -R₁-NR₆C(O)NR₆-, R₁-NR₆C(S)NR₆-, R₁-SO₂NR₆-, R₁-NR₆SO₂-, or R₁-NR₆C(O)O-, wherein the R₁-(C₁-C₃)alkylene, R₁-(C₂-C₃)alkenylene, or R₁-(C₂-C₃)alkynylene, is optionally substituted with one to three groups selected from R₅;

20 R₁ is hydrogen, halogen, -N(R₆)₂, -CN, (C₁-C₆)alkyl, halo(C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)alkoxy(C₁-C₆)alkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(C₁-C₃)alkyl, aryl(C₁-C₃)alkyl, heteroaryl(C₁-C₃)alkyl, heterocyclyl(C₁-C₃)alkyl, spiro cycloalkyl, or spiro heterocyclyl, each optionally substituted with one to three groups represented by R₅;

25 Y₂ is R_{2a}-(C₁-C₃)alkylene-, R_{2a}-C(O)-, R_{2a}-SO₂-, R_{2a}-S(O)-, R_{2a}-C(O)NR₆-, R_{2a}-SO₂NR₆-, R_{2a}-R₆C(O)-, or R_{2a}-NR₆SO₂-, wherein the R_{2a}-(C₁-C₃)alkylene is optionally substituted with one to three groups selected from R₅; or

Y₂ is R_{2b}-;

30 R_{2a} is hydrogen, halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)alkoxy(C₁-C₆)alkyl, cycloalkyl, aryl, aryloxy, heteroaryl, heteroaryloxy,

- heterocyclyl, cycloalkyl(C₁-C₃)alkyl, aryl(C₁-C₃)alkyl, heteroaryl(C₁-C₃)alkyl, heterocyclyl(C₁-C₃)alkyl, spiro cycloalkyl, or spiro heterocyclyl, each optionally substituted with one to three groups represented by R₅ or further selected from -N₃, aryloxy, aroyl, benzoate, tert-butyldimethylsiloxy, cylcoalkoxy, heterocyclyloxy, or heteroaryl;
- 5 R_{2b} is hydrogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy(C₁-C₆)alkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(C₁-C₃)alkyl, aryl(C₁-C₃)alkyl, heteroaryl(C₁-C₃)alkyl, heterocyclyl(C₁-C₃)alkyl, spiro cycloalkyl, or spiro heterocyclyl, each optionally substituted with one to three groups represented by R₅ or further selected from -N₃, aryloxy, aroyl, benzoate, tert-butyldimethylsiloxy, cylcoalkoxy, heterocyclyloxy, or heteroaryl;
- 10 Y₃ is R₃-, R₃-(C₁-C₃)alkylene, R₃-C(O)O-, R₃-OC(O)-, R₃-C(O)-, R₃-SO₂-, R₃-SO-, R₃-C(O)NR₆-, R₃-NR₆CO-, R₃-SO₂NR₆, or R₃-NR₆SO₂-, wherein the R₃-(C₁-C₃)alkylene is optionally substituted with R₅;
- 15 R₃ is hydrogen, halogen, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₁-C₆)alkoxy, (C₁-C₆)alkoxy(C₁-C₆)alkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(C₁-C₃)alkyl, aryl(C₁-C₃)alkyl, heteroaryl(C₁-C₃)alkyl, heterocyclyl(C₁-C₃)alkyl, spiro cycloalkyl, or spiro heterocyclyl, each optionally substituted with one to three groups represented by R₅;
- 20 R₄ is hydrogen or (C₁-C₆)alkyl optionally substituted with one to three groups represented by R₅; or
- R₄ and R₃, taken together, form a 5- to 7-membered heterocyclyl, heteroaryl, or spiro heterocyclyl, wherein each ring of the spiro heterocyclyl independently includes 3 to 7 atoms including Y₃ and the nitrogen atom to which R₄ is attached and is optionally substituted with 1 to 3 groups represented by R₅;
- 25 V and W are each independently selected from -NR₆-, -C(R₆)₂-, -O-, -S-, -S(O)-, and -S(O)₂-;
- each R₅ is independently selected from halogen, nitro, cyano, isocyano, hydroxy, (C₁-C₄)alkyl, (C₃-C₆)cycloalkyl, halo(C₁-C₄)alkyl, hydroxy(C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, H(CH₂CH₂O)_m-,
- 30

- 9 -

$\text{H}(\text{CH}_2\text{OCH}_2\text{O})_m-$, $\text{H}(\text{CH}_2\text{O})_m-$, $\text{H}(\text{CH}_2\text{OCH}_2\text{CH}_2\text{O})_n-$,
 $\text{H}(\text{CH}_2\text{CH}_2\text{OCH}_2\text{O})_n-$, $\text{H}(\text{OCH}_2\text{OCH}_2\text{CH}_2)_n-$, $\text{H}(\text{OCH}_2\text{CH}_2\text{OCH}_2)_n-$,
 $\text{H}(\text{CH}_2\text{OCH}_2\text{CH}_2\text{OCH}_2\text{O})_n-$, $\text{H}(\text{CH}_2\text{OCH}_2)-$, halo(C_1 - C_4)alkoxy, aryl,
 aryloxy, $\text{N}(\text{R}_6)_2$, $-\text{CO}_2\text{R}_6$, $-\text{OCOR}_6$, $-\text{NR}_6\text{CO}_2\text{R}_6$, $-\text{NR}_6\text{CO}_2\text{NR}_6$, $-\text{SO}_2\text{R}_6$,
 5 $-\text{SOR}_6$, $-\text{SO}_3\text{R}_6$, $-\text{NR}_6\text{SO}_2\text{R}_6$, $-\text{SO}_2\text{N}(\text{R}_6)_2$, morpholino, piperadyl, and
 piperazyl;

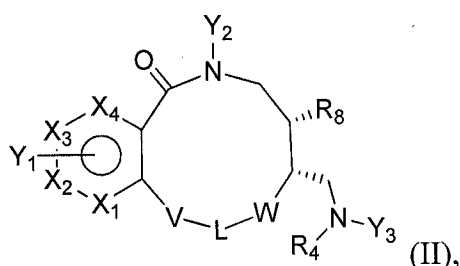
each R_6 is independently selected from hydrogen or (C_1 - C_4)alkyl;

R_8 is hydrogen or (C_1 - C_4)alkyl;

m is 1, 2, 3, 4, 5, or 6; and

10 n is 1, 2, or 3.

In a first aspect of the first embodiment, the compound is represented by the following structural formula:



or a pharmaceutically acceptable salt thereof. The values for the remaining variables
 15 are as defined in the first embodiment.

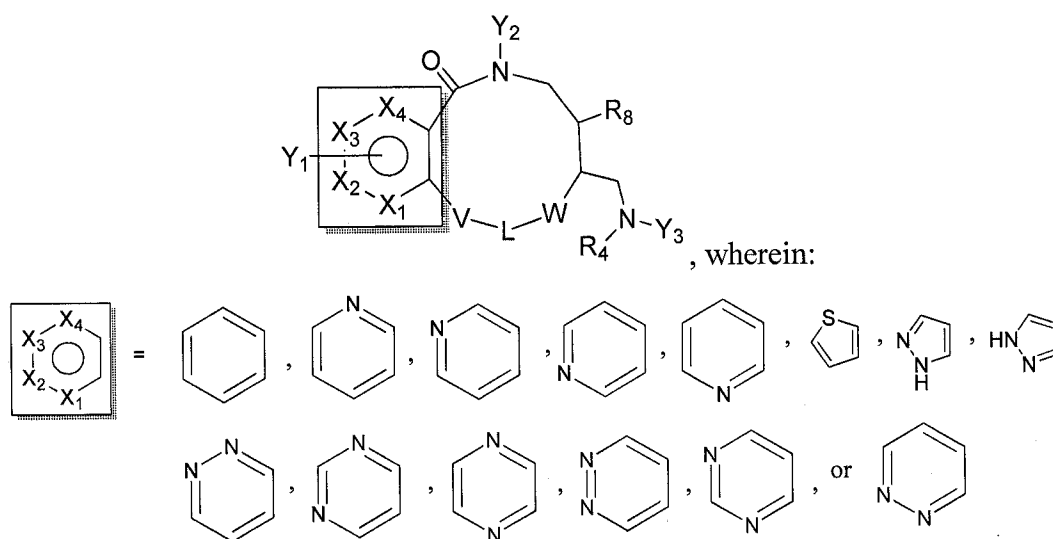
In a second aspect of the first embodiment, if X_1 , X_2 and X_4 are each CH, X_3 is C and Y_1 is $\text{R}_1\text{-NHC(O)NH-}$ and is bonded to X_3 , then R_1 is not unsubstituted phenyl. The values for the remaining variables are as defined in the first embodiment, or first aspect thereof.

20 In a third aspect of the first embodiment, Y_2 is not $-\text{CH}(\text{CH}_3)\text{CH}_2\text{OH}$. The values for the remaining variables are as defined in the first embodiment, or first or second aspects thereof.

In a fourth aspect of the first embodiment, Y_2 is $\text{R}_{2a}\text{-CH}_2\text{CH}_2\text{CH}(\text{CH}_3)-$ or $\text{R}_{2b}-$; $\text{R}_{2a}-$ is (C_1 - C_6)alkoxy, aryloxy, or heteroaryloxy, each optionally substituted
 25 with one to three groups represented by R_5 ; $\text{R}_{2b}-$ is $\text{CH}_3\text{CH}_2\text{CH}(\text{CH}_3)-$ and is optionally substituted with one group represented by R_5 or further selected from benzoate, tert-butyldimethylsiloxy, or heterocyclyloxy; and each R_5 is independently

selected from (C₁-C₄)alkoxy, H(CH₂CH₂O)_m-, H(CH₂OCH₂O)_m-, H(CH₂O)_m-, H(CH₂OCH₂CH₂O)_n-, H(CH₂CH₂OCH₂O)_n-, H(OCH₂OCH₂CH₂)_n-, H(OCH₂CH₂OCH₂)_n-, H(CH₂OCH₂CH₂OCH₂O)_n-, H(CH₂OCH₂)-, aryl and aryloxy. The values for the remaining variables are as defined in the first embodiment, or first through third aspects thereof.

In a fifth aspect of the first embodiment, X_1 , X_2 , X_3 and X_4 are defined as follows:



10 The values for the remaining variables are as defined in the first embodiment, or first
through fourth aspects thereof.

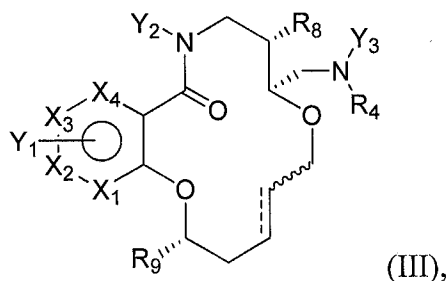
In a sixth aspect of the first embodiment, X_2 and X_3 are each CH. The values for the remaining variables are as defined in the first embodiment, or first through fifth aspects thereof.

15 In a seventh aspect of the first embodiment, X_2 is absent. The values for the remaining variables are as defined in the first embodiment, or first through sixth aspects thereof.

In an eighth aspect of the first embodiment, V is -O- or -NR₆-, W is -O-, and L is (C₁-C₅) alkylene or (C₁-C₅) alkenylene optionally substituted with methyl. The values for the remaining variables are as defined in the first embodiment, or first through seventh aspects thereof.

In a ninth aspect of the first embodiment, L is unsubstituted C₂-C₅ alkylene. The values for the remaining variables are as defined in the first embodiment, or first through eighth aspects thereof.

A second embodiment of the invention is a compound represented by the
5 following structural formula:



or a pharmaceutically acceptable salt thereof, wherein:

--- represents a single or a double bond; and

R₉ is hydrogen or (C₁-C₄)alkyl.

10 The values for the remaining variables are as defined in the first embodiment, or any aspect thereof.

In a first aspect of the second embodiment, R₉ is hydrogen or methyl. The values for the remaining variables are as defined in the first embodiment, or any aspect thereof, or in the second embodiment.

15 In a second aspect of the second embodiment, R₉ is hydrogen. The values for the remaining variables are as defined in the first embodiment, or any aspect thereof, or in the second embodiment, or first aspect thereof.

In a third aspect of the second embodiment, R₉ is methyl. The values for the remaining variables are as defined in the first embodiment, or any aspect thereof, or
20 in the second embodiment, or first or second aspect thereof.

In a fourth aspect of the second embodiment, R₈ is methyl and R₉ is methyl. The values for the remaining variables are as defined in the first embodiment, or any aspect thereof, or in the second embodiment, or first through third aspects thereof.

In a fifth aspect of the second embodiment, R₈ is hydrogen and R₉ is
25 hydrogen. The values for the remaining variables are as defined in the first embodiment, or any aspect thereof, or in the second embodiment, or first through fourth aspects thereof.

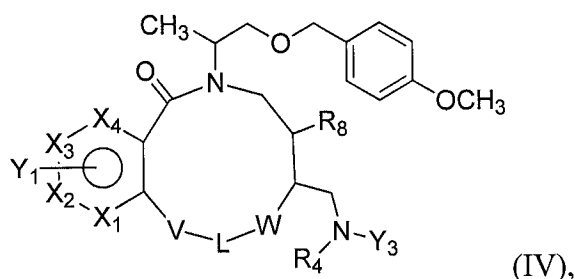
In a sixth aspect of the second embodiment, R₈ is hydrogen and R₉ is methyl. The values for the remaining variables are as defined in the first embodiment, or any aspect thereof, or in the second embodiment, or first through fifth aspects thereof.

In a seventh aspect of the second embodiment, R₈ is methyl and R₉ is hydrogen. The values for the remaining variables are as defined in the first embodiment, or any aspect thereof, or in the second embodiment, or first through sixth aspects thereof.

In an eighth aspect of the second embodiment, == represents a single bond. The values for the remaining variables are as defined in the first embodiment, or any aspect thereof, or in the second embodiment, or first through seventh aspects thereof.

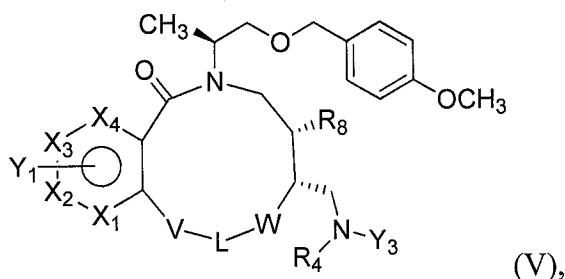
In a ninth aspect of the second embodiment, == represents a double bond. The values for the remaining variables are as defined in the first embodiment, or any aspect thereof, or in the second embodiment, or first through eighth aspects thereof.

A third embodiment of the invention is a compound represented by the following structural formula:



or a pharmaceutically acceptable salt thereof. The values for the remaining variables are as defined in the first or second embodiments, or any aspect thereof.

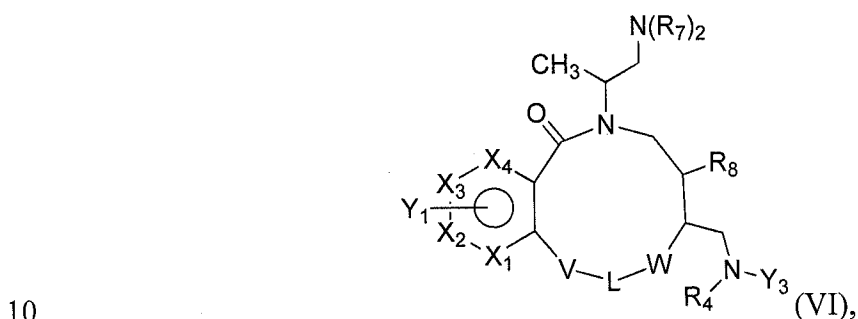
In a first aspect of the third embodiment, the compound of Structural Formula IV is represented by the following structural formula:



or a pharmaceutically acceptable salt thereof. The values for the remaining variables are as defined in the first or second embodiments, or any aspect thereof, or the third embodiment.

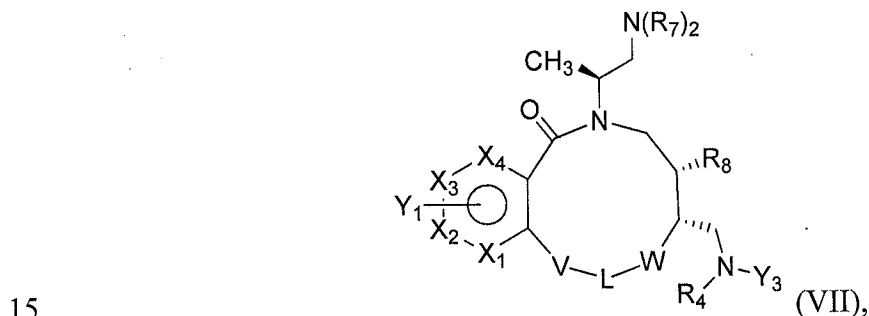
In a second aspect of the third embodiment, the compound of Structural
 5 Formula IV is selected from the group consisting of Compounds 1-4, 6-13, 15A, 15B, 16-22, 24-33, 35, 38, 40-44, 49, 50 and 134, or a pharmaceutically acceptable salt thereof.

A fourth embodiment of the invention is a compound represented by the following structural formula:



or a pharmaceutically acceptable salt thereof. The values for the remaining variables are as defined in the first or second embodiments, or any aspect thereof.

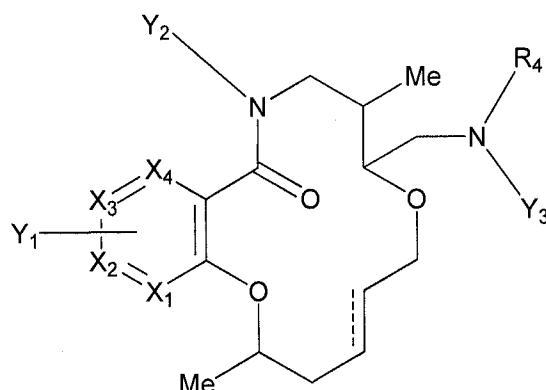
In a first aspect of the fourth embodiment, the compound of Structural
 Formula VI is represented by the following structural formula:



or a pharmaceutically acceptable salt thereof. The values for the remaining variables are as defined in the first or second embodiments, or any aspect thereof, or the fourth embodiment.

In a second aspect of the fourth embodiment, the compound of Structural
 20 Formula VI is selected from the group consisting of Compounds 100-105, ZZ and 111.

A fifth embodiment is a compound represented by the following structural formula:



, or a pharmaceutically acceptable

5 salt thereof, wherein

== represents a single or a double bond;

each of X_1 , X_2 , X_3 , and X_4 is independently N or CH, wherein at least two of X_1 , X_2 , X_3 , and X_4 are CH; wherein if Y_1 is present, then it is bonded to any one of X_1 , X_2 , X_3 , and X_4 , wherein the X_1 , X_2 , X_3 , and X_4 to which Y_1 is bonded to is C;

10 Y_1 is R_1 , R_1 -(C_1 - C_3)alkylene, R_1 -(C_2 - C_3)alkenylene, R_1 -(C_2 - C_3)alkynylene, R_1 - NR_6 -, R_1 -O-, R_1 -S-, R_1 -C(O)-, R_1 -C(S)-, R_1 -SO₂-, R_1 -S(O)-, R_1 -C(O)NR₆-, R_1 -NR₆C(O)-, R_1 -C(O)O-, R_1 -OC(O)-, R_1 -C(S)NR₆-, R_1 -NR₆C(S)-, R_1 -C(S)O-, R_1 -OC(S)-, R_1 -NR₆C(O)NR₆-, R_1 -NR₆C(S)NR₆-, R_1 -SO₂NR₆-, R_1 -NR₆SO₂-, or R_1 -NR₆C(O)O-, wherein the R_1 -(C_1 - C_3)alkylene, R_1 -(C_2 - C_3)alkenylene, or R_1 -(C_2 - C_3)alkynylene, is optionally substituted with one to three groups selected from R_5 ;

R_1 is hydrogen, halogen, -N(R_6)₂, -CN, (C_1 - C_6)alkyl, halo(C_1 - C_6)alkyl, (C_1 - C_6)alkoxy, (C_1 - C_6)alkoxy(C_1 - C_6)alkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(C_1 - C_3)alkyl, aryl(C_1 - C_3)alkyl, heteroaryl(C_1 - C_3)alkyl, heterocyclyl(C_1 - C_3)alkyl, spiro cycloalkyl, or spiro heterocyclyl, each optionally substituted with one to three groups represented by R_5 ;

20 Y_2 is R_{2a} -(C_1 - C_3)alkylene-, R_{2a} -C(O)-, R_{2a} -SO₂-, R_{2a} -S(O)-, R_{2a} -C(O)NR₆-, R_{2a} -SO₂NR₆-, R_{2a} -R₆C(O)-, or R_{2a} -NR₆SO₂-, wherein the R_{2a} -(C_1 - C_3)alkyl is optionally substituted with one to three groups selected from R_5 ; or

Y_2 is R_{2b} ;

R_{2a} is hydrogen, halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, (C_1-C_6) alkoxy (C_1-C_6) alkyl, cycloalkyl, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclyl, cycloalkyl (C_1-C_3) alkyl, aryl (C_1-C_3) alkyl, heteroaryl (C_1-C_3) alkyl, heterocyclyl (C_1-C_3) alkyl, spiro cycloalkyl, or spiro heterocycl, each optionally substituted with one to three groups represented by R_5 or further selected from $-N_3$, aryloxy, aroyl, benzoate, tert-butyldimethylsiloxy, or heteroaryl;

R_{2b} is hydrogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy (C_1-C_6) alkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, cycloalkyl (C_1-C_3) alkyl, aryl (C_1-C_3) alkyl, heteroaryl (C_1-C_3) alkyl, heterocyclyl (C_1-C_3) alkyl, spiro cycloalkyl, or spiro heterocycl, each optionally substituted with one to three groups represented by R_5 or further selected from $-N_3$, aryloxy, aroyl, benzoate, tert-butyldimethylsiloxy, or heteroaryl;

Y_3 is R_3 -, R_3 -(C_1-C_3)alkylene, R_3 -C(O)O-, R_3 -OC(O)-, R_3 -C(O)-, R_3 -SO₂-, R_3 --SO-, R_3 -C(O)NR₆-, R_3 -NR₆CO-, R_3 -SO₂NR₆, or R_3 -NR₆SO₂-, wherein the R_3 -(C_1-C_3)alkylene is optionally substituted with R_5 ;

R_3 is hydrogen, halogen, (C_1-C_6) alkyl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, (C_1-C_6) alkoxy, (C_1-C_6) alkoxy (C_1-C_6) alkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, cycloalkyl (C_1-C_3) alkyl, aryl (C_1-C_3) alkyl, heteroaryl (C_1-C_3) alkyl, heterocyclyl (C_1-C_3) alkyl, spiro cycloalkyl, or spiro heterocycl, each optionally substituted with one to three groups represented by R_5 ;

R_4 is hydrogen, or (C_1-C_6) alkyl optionally substituted with one to three groups represented by R_5 ; or

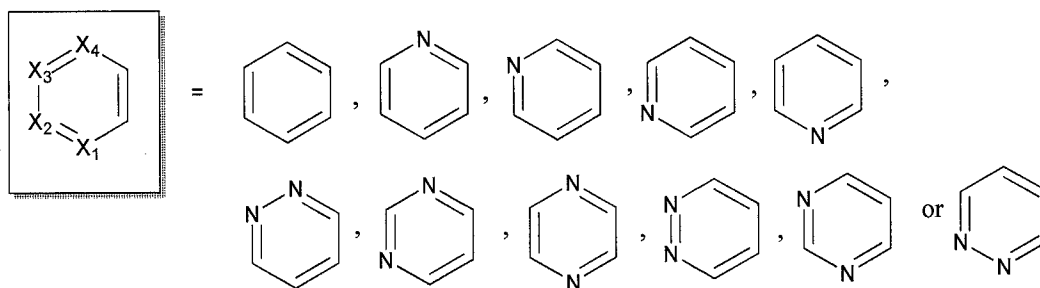
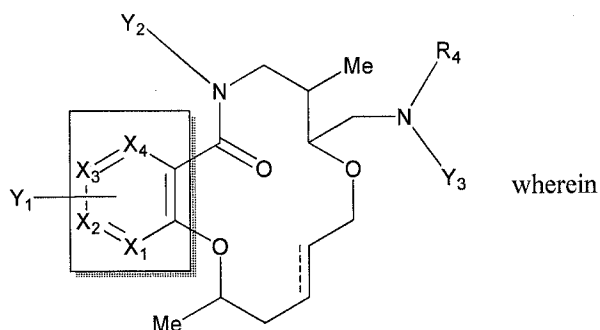
R_4 and R_3 , taken together form a 5- to 7-membered heterocyclyl, heteroaryl, or spiro heterocyclyl, wherein each ring of the spiro heterocyclyl formed independently includes 3 to 7 atoms, with Y_3 and the nitrogen atom to which R_4 is attached, wherein the ring formed is optionally substituted with 1 to 3 groups represented by R_5 ;

each R_5 is independently selected from halogen, nitro, cyano, isocyano, hydroxy, (C_1-C_4) alkyl, (C_3-C_6) cycloalkyl, halo (C_1-C_4) alkyl, hydroxy (C_1-C_4) alkyl, (C_1-C_4) alkoxy, (C_1-C_4) alkoxy (C_1-C_4) alkyl, $H(CH_2CH_2O)_m$ -, $H(CH_2OCH_2O)_m$ -,

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- $H(CH_2O)_m-$, $H(CH_2OCH_2CH_2O)_n-$; $H(CH_2CH_2OCH_2O)_n-$; $H(OCH_2OCH_2CH_2)_n-$;
 $H(OCH_2CH_2OCH_2)_n-$; $H(CH_2OCH_2CH_2OCH_2O)_n-$; $H(CH_2OCH_2)-$, halo(C₁-C₄)alkoxy,
 aryl, aryloxy, N(R₆)₂, -CO₂R₆, -OCOR₆, -NR₆CO₂R₆, -NR₆CO₂NR₆,
 SO₂R₆, SOR₆, SO₃R₆, NR₆SO₂R₆, SO₂N(R₆)₂, morpholino, piperadyl, and
 5 piperazyl;
 each R₆ is independently selected from hydrogen or (C₁-C₄)alkyl;
 m is 1, 2, 3, 4, 5, or 6; and
 n is 1, 2, or 3.

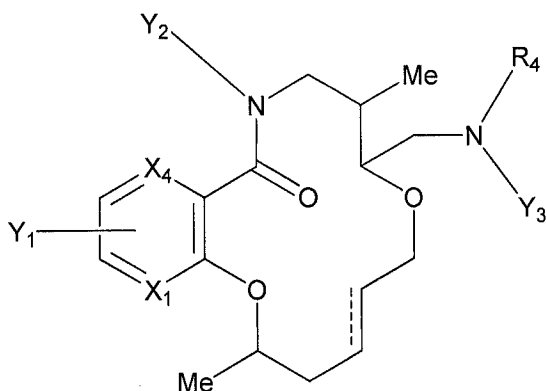
Specifically, X₁, X₂, X₃, and X₄ are defined as follows:



10

In a first aspect of the fifth embodiment, the compound is represented by the following structural formula:

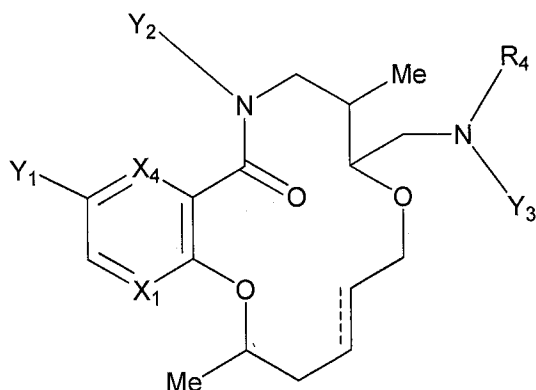
- 17 -



, or a pharmaceutically acceptable salt

thereof, wherein the values for the remaining variables are as defined in the first through fourth embodiments, or any aspect thereof, or the fifth embodiment.

In a second aspect of the fifth embodiment, the compound is represented by
 5 the following structural formula:

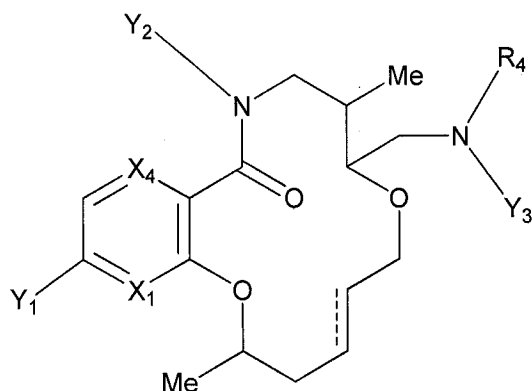


, or a pharmaceutically acceptable salt

thereof, wherein the values for the remaining variables are as defined in the first through fourth embodiments, or any aspect thereof, or the fifth embodiment, or first aspect thereof.

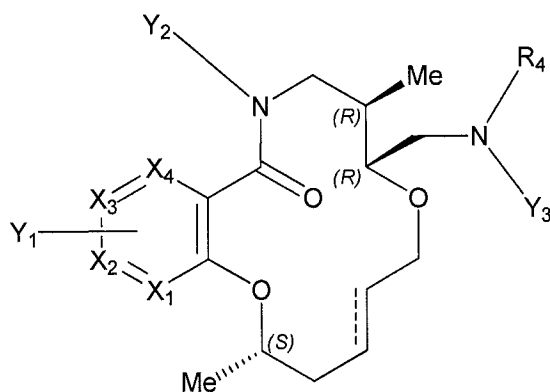
10 In a third aspect of the fifth embodiment, the compound is represented by the following structural formula:

- 18 -



, or a pharmaceutically acceptable salt thereof, wherein the values for the remaining variables are as defined in the first through fourth embodiments, or any aspect thereof, or the fifth embodiment, or first or second aspect thereof.

- 5 In a fourth aspect of the fifth embodiment, the compound is represented by the following structural formula:



- , or a pharmaceutically acceptable salt thereof, wherein the values for the remaining variables are as defined in the first through fourth embodiments, or any aspect thereof, or the fifth embodiment, or first
10 through third aspects thereof.

- In a fifth aspect of the fifth embodiment, the compound is represented by any one of the structural formulas of the first through fourth embodiments, or any aspect thereof, or the fifth embodiment, or the first, second, third, or fourth aspect thereof, wherein X_1 is N and X_4 is N; X_1 is N and X_4 is CH; X_1 is CH and X_4 is CH; or X_1 is
15 N and X_4 is N, wherein the values for the remaining variables are as defined in the first through fourth embodiments, or any aspect thereof, or the fifth embodiment, or first through fourth aspects thereof.

In a sixth aspect of the fifth embodiment, the compound is represented by any one of the structural formulas of the first through fourth embodiments, or any aspect thereof, or the fifth embodiment or the first, second, third, or fourth aspect of the fifth embodiment, --- represents a single bond, wherein the values for the
5 remaining variables are as defined in the first through fourth embodiments, or any aspect thereof, or the fifth embodiment, or first through fifth aspects thereof.

In a seventh aspect of the fifth embodiment, the compound is represented by any one of the structural formulas of the first through fourth embodiments, or any aspect thereof, or the fifth embodiment or the first, second, third, or fourth aspect of
10 the fifth embodiment, = represents a double bond, wherein the values for the remaining variables are as defined in the first through fourth embodiments, or any aspect thereof, or the fifth embodiment, or first through fifth aspects thereof.

In an eighth aspect of the fifth embodiment, the compound is represented by any one of the structural formulas of the first through fourth embodiments, or any
15 aspect thereof, or the fifth embodiment or the first, second, third, or fourth aspect of the fifth embodiment and Y_1 is R_1 , $R_1\text{-CH}_2\text{-}$, $R_1\text{-NR}_6\text{-}$, $R_1\text{-C(O)NR}_6\text{-}$, $R_1\text{-C(O)O-}$, $R_1\text{-NR}_6\text{C(O)NR}_6\text{-}$, or $R_1\text{-SO}_2\text{NR}_6\text{-}$, wherein the values for the remaining variables are as defined in the first through fourth embodiments, or any aspect thereof, or the fifth embodiment, or first through seventh aspects thereof.

In a ninth aspect of the fifth embodiment, the compound is represented by any one of the structural formulas of the first through fourth embodiments, or any
20 aspect thereof, or the fifth embodiment or the first, second, third, or fourth aspect of the fifth embodiment and R_1 is hydrogen, halogen, $\text{-N(R}_6)_2$, -CN , $(\text{C}_1\text{-C}_6)\text{alkyl}$, $\text{halo(C}_1\text{-C}_6)\text{alkyl}$, cycloalkyl , aryl or heteroaryl , each optionally substituted with one
25 to three groups represented by R_5 , wherein the values for the remaining variables are as defined in the first through fourth embodiments, or any aspect thereof, or the fifth embodiment, or first through eighth aspects thereof.

In a tenth aspect of the fifth embodiment, the compound is represented by any one of the structural formulas of the first through fourth embodiments, or any
30 aspect thereof, or the fifth embodiment or the first, second, third, or fourth aspect of the fifth embodiment and Y_2 is R_{2b} or Y_2 is $R_{2a}\text{-(C}_1\text{-C}_2\text{alkylene)}$, wherein the values

for the remaining variables are as defined in the first through fourth embodiments, or any aspect thereof, or the fifth embodiment, or first through ninth aspects thereof.

In an eleventh aspect of the fifth embodiment, the compound is represented by any one of the structural formulas of the first through fourth embodiments, or any aspect thereof, or the fifth embodiment or the first, second, third, or fourth aspect of the fifth embodiment; R_{2a} is (C₁-C₆)alkyl, (C₁-C₆)alkoxy, aryl, aryl(C₁-C₃)alkyl, aryloxy, heteroaryl, heteroaryl(C₁-C₃)alkyl, or heteroaryloxy, each optionally substituted with one to three groups represented by R₅ or further selected from -N₃, aryloxy, heteroaryloxy, benzoate, tert-butyldimethylsiloxy, or heteroaryl; and R_{2b} is hydrogen, (C₁-C₆)alkyl, aryl, heteroaryl, each optionally substituted with one to three groups represented by R₅ or further selected from -N₃, aryloxy, heteroaryloxy, benzoate, tert-butyldimethylsiloxy, or heteroaryl, wherein the values for the remaining variables are as defined in the first through fourth embodiments, or any aspect thereof, or the fifth embodiment, or first through tenth aspects thereof. In a specific aspect of the eleventh aspect, R_{2a} and R_{2b} are each optionally substituted with one to three groups represented by R₅ or further selected from -N₃, pyridinoxy, benzoxy, p-methoxybenzoxy, benzoate, tert-butyldimethylsiloxy, or heteroaryl.

In a twelfth aspect of the fifth embodiment, the compound is represented by any one of the structural formulas of the first through fourth embodiments, or any aspect thereof, or the fifth embodiment or the first, second, third, or fourth aspect of the fifth embodiment and Y₃ is R₃, -CH₂-, -C(O)O-, -C(O)-, -SO₂-, or -C(O)NR₆-, wherein the values for the remaining variables are as defined in the first through fourth embodiments, or any aspect thereof, or the fifth embodiment, or first through eleventh aspects thereof.

In a thirteenth aspect of the fifth embodiment, the compound is represented by any one of the structural formulas of the first through fourth embodiments, or any aspect thereof, or the fifth embodiment or the first, second, third, or fourth aspect of the fifth embodiment and R₃ is hydrogen, (C₁-C₆)alkyl, (C₁-C₆)alkenyl, (C₁-C₆)alkoxy, (C₁-C₆)alkoxy(C₁-C₆)alkyl, (C₃-C₇)cycloalkyl, phenyl, or heteroaryl, each optionally substituted with one to three groups represented by R₅, wherein the values for the remaining variables are as defined in the first through fourth

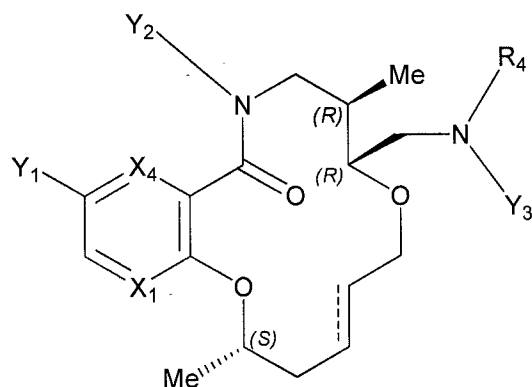
embodiments, or any aspect thereof, or the fifth embodiment, or first through twelfth aspects thereof.

In a fourteenth aspect of the fifth embodiment, the compound is represented by any one of the structural formulas of the first through fourth embodiments, or any aspect thereof, or the fifth embodiment or the first, second, third, or fourth aspect of the fifth embodiment and R_4 is hydrogen, methyl, ethyl, propyl, isopropyl, butyl or tert-butyl, wherein the values for the remaining variables are as defined in the first through fourth embodiments, or any aspect thereof, or the fifth embodiment, or first through thirteenth aspects thereof. In a specific aspect of the fourteenth aspect, R_4 is methyl.

In a fifteenth aspect of the fifth embodiment, the compound is represented by any one of the structural formulas of the first through fourth embodiments, or any aspect thereof, or the fifth embodiment or the first, second, third, or fourth aspect of the fifth embodiment and each R_5 is selected from fluoro, chloro, cyano, hydroxy, (C₁-C₄)alkyl, halo(C₁-C₄)alkyl, hydroxy(C₁-C₄)alkyl, (C₁-C₄)alkoxy, H(CH₂OCH₂CH₂OCH₂O)-, H(CH₂OCH₂)-, NH₂, N(CH₃)₂, NHCH₃, CO₂R₆, -NR₆CO₂R₆, -NR₆CO₂NR₆, SO₂R₆, NR₆SO₂R₆, and SO₂N(R₆)₂, wherein the values for the remaining variables are as defined in the first through fourth embodiments, or any aspect thereof, or the fifth embodiment, or first through fourteenth aspects thereof.

A sixth embodiment is a compound represented by the following structural formula, wherein the compound is represented by the following structural formula:

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, or a pharmaceutically acceptable

salt thereof, wherein:

==== represents a single or a double bond;

each of X₁ and X₄ is independently N or CH;

- 5 Y₁ is R₁, R₁-CH₂-, R₁-NR₆-, R₁-C(O)NR₆-, R₁--C(O)O-, R₁-NR₆C(O)NR₆-, or R₁-SO₂NR₆-;

R₁ is hydrogen, halogen, -N(R₆)₂, -CN, (C₁-C₆)alkyl, halo(C₁-C₆)alkyl, cycloalkyl, aryl or heteroaryl, each optionally substituted with one to three groups represented by R₅;

- 10 Y₂ is R_{2b} or Y₂ is R_{2a}-(C₁-C₂alkyl)-;

R_{2a} is (C₁-C₆)alkyl, (C₁-C₆)alkoxy, aryl, aryl(C₁-C₃)alkyl, aryloxy, heteroaryl, heteroaryl(C₁-C₃)alkyl, or heteroaryloxy, each optionally substituted with one to three groups represented by R₅ or further selected from -N₃, pyridinoxy, benzoxy, p-methoxybenzoxy, benzoate, tert-butyldimethylsiloxy, or heteroaryl;

- 15 R_{2b} is hydrogen, (C₁-C₆)alkyl, aryl, heteroaryl, each optionally substituted with one to three groups represented by R₅ or further selected from -N₃, pyridinoxy, benzoxy, p-methoxybenzoxy, benzoate, tert-butyldimethylsiloxy, or heteroaryl;

Y₃ is R₃, -CH₂-, -C(O)O-, -C(O)-, -SO₂-, or -C(O)NR₆-;

R₃ is hydrogen, (C₁-C₆)alkyl, (C₁-C₆)alkenyl, (C₁-C₆)alkoxy, (C₁-C₆)alkoxy(C₁-

- 20 C₆)alkyl, (C₃-C₇)cycloalkyl, phenyl, or heteroaryl, each optionally substituted with one to three groups represented by R₅;

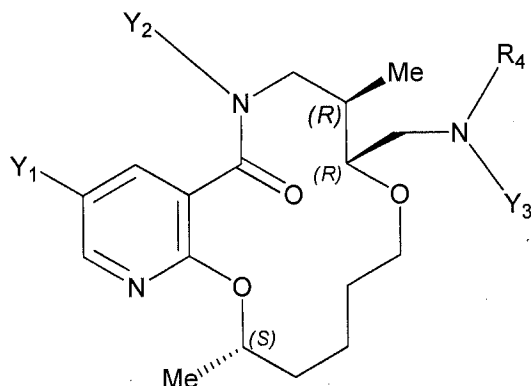
R₄ is hydrogen, methyl, ethyl, propyl, isopropyl, butyl or tert-butyl; and

R₅ is selected from fluoro, chloro, cyano, hydroxy, (C₁-C₄)alkyl, halo(C₁-C₄)alkyl, hydroxy(C₁-C₄)alkyl, (C₁-C₄)alkoxy, H(CH₂OCH₂CH₂OCH₂O)-; H(CH₂OCH₂)-,

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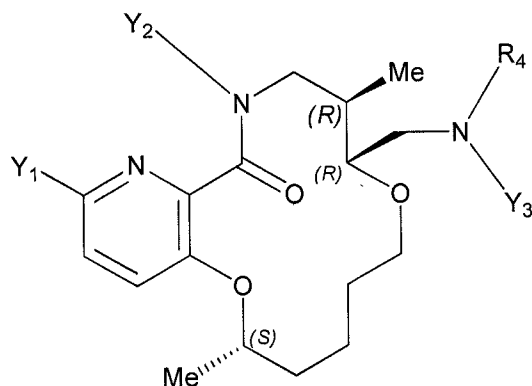
$\text{H}(\text{CH}_2\text{OCH}_2\text{O})-$, NH_2 , $\text{N}(\text{CH}_3)_2$, NHCH_3 , CO_2R_6 , $-\text{NR}_6\text{CO}_2\text{R}_6$, $-\text{NR}_6\text{CO}_2\text{NR}_6$, SO_2R_6 , $\text{NR}_6\text{SO}_2\text{R}_6$, and $\text{SO}_2\text{N}(\text{R}_6)_2$.

In a first aspect of the sixth embodiment, the compound is represented by the following structural formula:



5 , or a pharmaceutically acceptable salt thereof, wherein the values for the remaining variables are as defined in the first through fifth embodiments, or any aspect thereof, or the sixth embodiment.

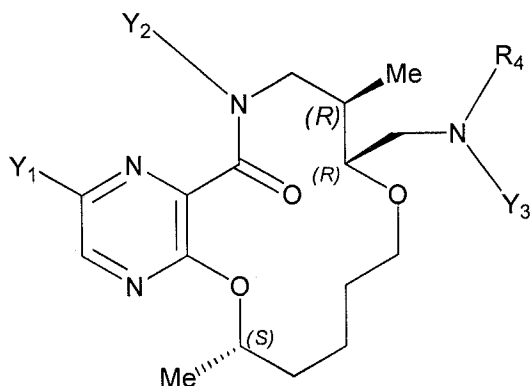
In a second aspect of the sixth embodiment, the compound is represented by the following structural formula:



10 , or a pharmaceutically acceptable salt thereof, wherein the values for the remaining variables are as defined in the first through fifth embodiments, or any aspect thereof, or the sixth embodiment, or first aspect thereof.

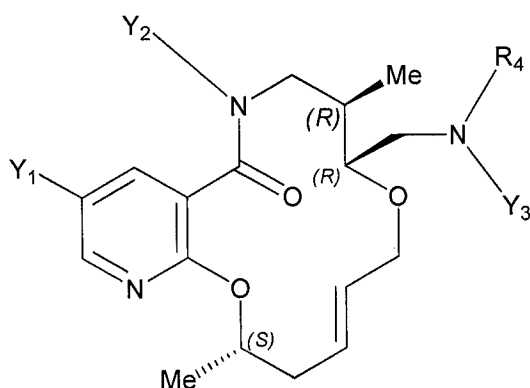
15 In a third aspect of the sixth embodiment, the compound is represented by the following structural formula:

- 24 -



, or a pharmaceutically acceptable salt thereof, wherein the values for the remaining variables are as defined in the first through fifth embodiments, or any aspect thereof, or the sixth embodiment, or first or second aspect thereof.

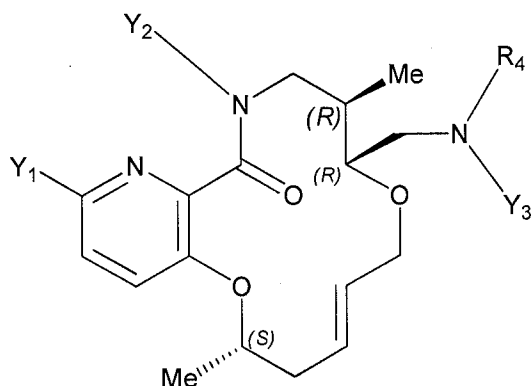
- 5 In a fourth aspect of the sixth embodiment, the compound is represented by the following structural formula:



- , or a pharmaceutically acceptable salt thereof, wherein the values for the remaining variables are as defined in the first through fifth embodiments, or any aspect thereof, or the sixth embodiment, or first
10 through third aspects thereof.

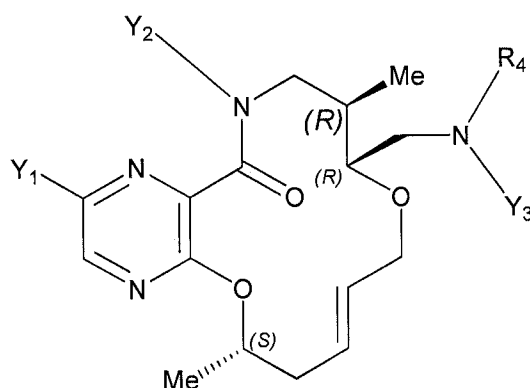
In a fifth aspect of the sixth embodiment, the compound is represented by the following structural formula:

- 25 -



, or a pharmaceutically acceptable salt thereof, wherein the values for the remaining variables are as defined in the first through fifth embodiments, or any aspect thereof, or the sixth embodiment, or first through fourth aspects thereof.

- 5 In a sixth aspect of the sixth embodiment, the compound is represented by the following structural formula:



- , or a pharmaceutically acceptable salt thereof, wherein the values for the remaining variables are as defined in the first through fifth embodiments, or any aspect thereof, or the sixth embodiment, or first through fifth aspects thereof.
- 10

- In a seventh aspect of the sixth embodiment, the compound is represented by any one of the structural formulas of the first through fifth embodiments, or any aspect thereof, or the sixth embodiment or the first, second, third, fourth, fifth, or sixth aspect of the sixth embodiment and Y₁ is R₁, R₁-NH-, R₁-NHC(O)NH-, R₁-C(O)NH-, or R₁-SO₂NH-, wherein the values for the remaining variables are as defined in the first through fifth embodiments, or any aspect thereof, or the sixth embodiment, or first through sixth aspects thereof.
- 15

In an eighth aspect of the sixth embodiment, the compound is represented by any one of the structural formulas of the first through fifth embodiments, or any aspect thereof, or the sixth embodiment or the first, second, third, fourth, fifth, or sixth aspect of the sixth embodiment and R_1 is hydrogen, fluoro, $-CF_3$, $-NH_2$, $-CN$,
5 (C₁-C₃)alkyl, phenyl, isoxazolyl, benzoxazolyl, imidazolyl, pyridine, or thiophene, each optionally substituted with one to three groups represented by R_5 , or R_1-SO_2NH- , wherein the values for the remaining variables are as defined in the first through fifth embodiments, or any aspect thereof, or the sixth embodiment, or first through seventh aspects thereof.

10 In a ninth aspect of the sixth embodiment, the compound is represented by any one of the structural formulas of the first through fifth embodiments, or any aspect thereof, or the sixth embodiment or the first, second, third, fourth, fifth, or sixth aspect of the sixth embodiment and Y_2 is R_{2b} , wherein the values for the remaining variables are as defined in the first through fifth embodiments, or any
15 aspect thereof, or the sixth embodiment, or first through eighth aspects thereof.

In a tenth aspect of the sixth embodiment, the compound is represented by any one of the structural formulas of the first through fifth embodiments, or any aspect thereof, or the sixth embodiment or the first, second, third, fourth, fifth, or sixth aspect of the sixth embodiment and R_{2b} is ethyl or 1-methylethyl, optionally
20 substituted with p-methoxybenzoxy, (C₁-C₄)alkoxy, hydroxyl, or dimethylamino, wherein the values for the remaining variables are as defined in the first through fifth embodiments, or any aspect thereof, or the sixth embodiment, or first through ninth aspects thereof.

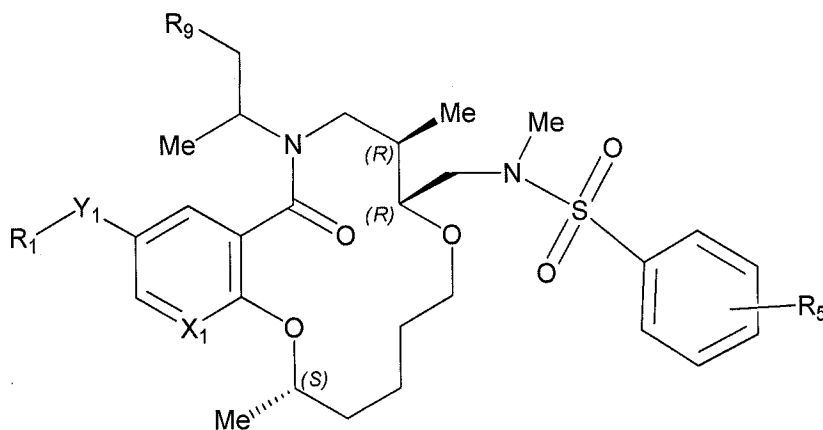
In an eleventh aspect of the sixth embodiment, the compound is represented
25 by any one of the structural formulas of the first through fifth embodiments, or any aspect thereof, or the sixth embodiment or the first, second, third, fourth, fifth, or sixth aspect of the sixth embodiment and Y_3 is R_3-SO_2- , wherein the values for the remaining variables are as defined in the first through fifth embodiments, or any aspect thereof, or the sixth embodiment, or first through tenth aspects thereof.

30 In a twelfth aspect of the sixth embodiment, the compound is represented by any one of the structural formulas of the first through fifth embodiments, or any

aspect thereof, or the sixth embodiment or the first, second, third, fourth, fifth, or sixth aspect of the sixth embodiment and R₃ is phenyl optionally substituted with fluoro, chloro, methyl, methoxy, trifluoromethyl, or carboxy, wherein the values for the remaining variables are as defined in the first through fifth embodiments, or any aspect thereof, or the sixth embodiment, or first through eleventh aspects thereof.

In a thirteenth aspect of the sixth embodiment, the compound is represented by any one of the structural formulas of the first through fifth embodiments, or any aspect thereof, or the sixth embodiment or the first, second, third, fourth, fifth, or sixth aspect of the sixth embodiment and R₄ is hydrogen or methyl, wherein the values for the remaining variables are as defined in the first through fifth
10 embodiments, or any aspect thereof, or the sixth embodiment, or first through twelfth aspects thereof. In a specific aspect of the thirteenth aspect, R₄ is methyl.

A seventh embodiment is a compound represented by the following structural formula:



15, or a

pharmaceutically acceptable salt thereof, wherein:

X_1 is N or CH;

R₁ is hydrogen, fluoro, (C₁-C₃)alkyl, phenyl or isoxazolyl, wherein the phenyl or isoxazolyl each are optionally substituted with one to two methyl groups;

20 Y₁ is R₁ or R₁-NHC(O)NH-;

R₉ is p-methoxybenzoxy, butoxy, hydroxy, methoxymethoxy, 2-methoxyethoxy, azido and dimethylamine, and

R₅ is fluoro, chloro, methyl, methoxy, or trifluoromethyl.

In a specific aspect of the first through seventh embodiments, the compound is not selected from any one of Compounds 137-201.

Another embodiment of the invention is a pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and a compound of any one of the first through seventh embodiments, or any aspect thereof.

Another embodiment of the invention is a method of treating malaria in a subject in need thereof, comprising administering to the subject an effective amount of a compound of any one of the first through seventh embodiments, or any aspect thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound of any one of the first through seventh embodiments, or any aspect thereof, or a pharmaceutically acceptable salt thereof.

The compounds of the invention may be present in the form of pharmaceutically acceptable salts. For use in medicines, the salts of the compounds of the invention refer to non-toxic "pharmaceutically acceptable salts."

Pharmaceutically acceptable salt forms include pharmaceutically acceptable acidic/anionic or basic/cationic salts.

Pharmaceutically acceptable acidic/anionic salts include, the acetate, benzenesulfonate, benzoate, bicarbonate, bitartrate, bromide, calcium edetate, camsylate, carbonate, chloride, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, glyceptate, gluconate, glutamate, glycolylarsanilate, hexylresorcinate, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, malate, maleate, malonate, mandelate, mesylate, methylsulfate, mucate, napsylate, nitrate, pamoate, pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, sulfate, hydrogensulfate, tannate, tartrate, teoclate, tosylate, and triethiodide salts.

Pharmaceutically acceptable basic/cationic salts include, the sodium, potassium, calcium, magnesium, diethanolamine, N-methyl-D-glucamine, L-lysine, L-arginine, ammonium, ethanolamine, piperazine and triethanolamine salts.

The disclosed compounds can be used alone (i.e., as a monotherapy) or in combination with another therapeutic agent effective for treating malaria.

Alternatively, a pharmaceutical composition of the invention may comprise an antimalarial compound disclosed herein, or a pharmaceutical salt thereof, as the only pharmaceutically active agent in the pharmaceutical composition. The disclosed macrolactam compounds can be used alone or in a combination therapy with one or more additional agents for the treatment of malaria.

A pharmaceutical composition of the invention may, alternatively or in addition to a macrolactam antimalarial compound disclosed herein, comprise a pharmaceutically acceptable salt of a macrolactam compound disclosed herein, or a prodrug or pharmaceutically active metabolite of such a compound or salt and one or more pharmaceutically acceptable carriers therefore. Alternatively, a pharmaceutical composition of the invention may comprise an antimalarial compound disclosed herein or a pharmaceutical salt thereof as the only pharmaceutically active agent in the pharmaceutical composition.

The invention includes a therapeutic method for treating malaria in a subject in need thereof comprising administering to the subject in need thereof an effective amount of a macrolactam compound disclosed herein, or a pharmaceutically acceptable salt thereof or a composition thereof (e.g., a pharmaceutical composition comprising a macrolactam compound and a pharmaceutically- acceptable carrier). Compounds disclosed herein can be used in the treatment of malaria. Thus, in one embodiment, the invention relates to the use of a compound disclosed herein for the treatment of malaria in a subject in need thereof. In other embodiments, the invention relates to the use of a compound disclosed herein in the treatment of malaria and the use of a compound disclosed herein in the manufacture of a medicament for the treatment of malaria. As used herein, "treating" or "treatment" includes both therapeutic and prophylactic treatment. Therapeutic treatment includes reducing the symptoms associated with a disease or condition and/or increasing the longevity of a subject with the disease or condition. Prophylactic treatment includes delaying the onset of a disease or condition in a subject at risk of developing the disease or condition or reducing the likelihood that a subject will then develop the disease or condition in a subject that is at risk for developing the disease or condition.

As used herein, an “effective amount” is an amount sufficient to achieve a desired effect under the conditions of administration, *in vitro*, *in vivo* or *ex vivo*, such as, for example, an amount sufficient to treat malaria in a subject. The effectiveness of a compound can be determined by suitable methods known by those of skill in the art including those described herein.

As defined herein, a “therapeutically effective amount” is an amount sufficient to achieve a desired therapeutic or prophylactic effect in a subject in need thereof under the conditions of administration, such as, for example, an amount sufficient treat malaria in a subject. The effectiveness of a therapy can be determined by suitable methods known by those of skill in the art.

An embodiment of the invention includes administering an antimalarial compound disclosed herein, or composition thereof, in a combination therapy with one or more additional agents for the treatment of malaria. Agents for the treatment of malaria include quinine, atovaquone, chloroquine, cycloguanil, hydroxychloroquine, amodiaquine, pyrimethamine, sulphadoxine, proguanil, mefloquine, halofantrine, pamaquine, primaquine, artemesinin, artemether, artesunate, arteminol, lumefantrine, dihydroartemisinin, piperaquine, artether, doxycycline and clindamycin.

The compounds of the present invention can be prepared and administered in a wide variety of oral and parenteral dosage forms. Thus, the compounds of the present invention can be administered by injection, that is, intravenously, intramuscularly, intracutaneously, subcutaneously, intraduodenally, or intraperitoneally. Additionally, the compounds of the present invention can be administered intranasally or transdermally. It will be obvious to those skilled in the art that the following dosage forms may comprise as the active ingredient, either compounds or a corresponding pharmaceutically acceptable salt of a compound of the present invention.

For preparing pharmaceutical compositions from the compounds of the present invention, pharmaceutically acceptable carriers can either be solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more

substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material. In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active ingredient.

5 In tablets, the active ingredient is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

 The powders and tablets preferably contain from about one to about seventy percent of the active ingredient. Suitable carriers are magnesium carbonate,
10 magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium caboxymethylcellulose, a low-melting wax, cocoa butter, and the like. Tablets, powders, cachets, lozenges, fast-melt strips, capsules and pills can be used as solid dosage forms containing the active ingredient suitable for oral administration.

15 Suitable for enteral administration are also suppositories that consist of a combination of the active ingredient and a suppository base. Suitable as suppository bases are, for example, natural or synthetic triglycerides, paraffins, polyethylene glycols or higher alkanols. It is also possible to use gelatin rectal capsules that contain a combination of the active ingredient and a base material; suitable base
20 materials are, for example, liquid triglycerides, polyethylene glycols or paraffin hydrocarbons. For preparing suppositories, a low-melting wax, such as a mixture of fatty acid glycerides or cocoa butter, is first-melted and the active ingredient is dispersed homogeneously therein, as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

25 Liquid form preparations include solutions, suspensions, retention enemas, and emulsions, for example, water or water propylene glycol solutions. For parenteral injection, liquid preparations can be formulated in solution in aqueous polyethylene glycol solution.

 Aqueous solutions suitable for oral administration can be prepared by
30 dissolving the active ingredient in water and adding suitable colorants, flavors, stabilizing, and thickening agents as desired. Aqueous suspensions for oral

administration can be prepared by dispersing the finely divided active ingredient in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.

5 The pharmaceutical composition is preferably in unit dosage form. In such form, the composition is subdivided into unit doses containing appropriate quantities of the active ingredient. The unit dosage form can be a packaged preparation, the package containing discrete quantities of, for example, tablets, powders, and capsules in vials or ampules. Also, the unit dosage form can be a tablet, cachet, 10 capsule, or lozenge itself, or it can be the appropriate amount of any of these in packaged form.

 The dosages may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the compound being employed. Determination of the proper dosage for a particular situation is within the skill in the 15 art. Also, the pharmaceutical composition may contain, if desired, other compatible therapeutic agents.

DEFINITIONS

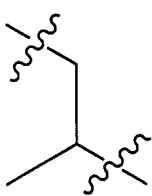
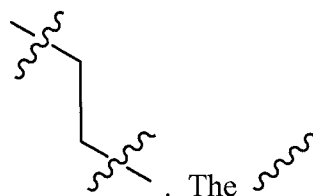
 The term "alkyl", used alone or as part of a larger moiety such as "arylalkyl" or "haloalkyl" means a straight or branched hydrocarbon radical having, for 20 example, 1-10 carbon atoms, specifically 1-6 carbon atoms, or even more specifically, 1-3 carbon atoms, and includes, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, i-pentyl, n-hexyl, n-heptyl, n-octyl, n-nonyl, n-decyl and the like.

 An "alkenyl group" is an alkyl group in which at least a pair of adjacent 25 methylenes is replaced with $-\text{CH}=\text{CH}-$.

 An "alkynyl group" is an alkyl group in which at least a pair of adjacent methylenes is replaced with $-\text{C}\equiv\text{C}-$.

 "Alkylene" means an optionally substituted saturated aliphatic branched or straight-chain divalent hydrocarbon radical having the specified number of carbon 30 atoms. Thus, "(C₁-C₃)alkylene" means a divalent saturated aliphatic radical having

from 1- 3 carbon atoms in a linear arrangement, e.g., $-(\text{CH}_2)_n-$, where n is an integer from 1 to 3, “(C₁-C₃)alkylene” includes methylene, ethylene, propylene, butylene, pentylene and hexylene. Alternatively, “(C₁-C₃)alkylene” means a divalent saturated radical having from 1-3 carbon atoms in a branched arrangement,
 5 for example: $-(\text{CH}_2\text{CH}(\text{CH}_3))-$, $-(\text{C}(\text{CH}_3)_2)-$, and the like. A specific branched C₃-

alkylene is  and a specific C₂-alkylene is . The  indicates the point of connection to the remainder of the molecule.

An “alkenylene” is an alkylene group in which at least a pair of adjacent methylenes is replaced with $-\text{CH}=\text{CH}-$.

10 An “alkynylene group” is an alkylene group in which at least a pair of adjacent methylenes is replaced with $-\text{C}\equiv\text{C}-$.

The term “alkoxy” means an alkyl radical attached through an oxygen linking atom. “(C₁-C₄)-alkoxy” includes methoxy, ethoxy, propoxy, and butoxy.

“Aryl”, used alone or as part of a larger moiety as in “arylalkyl”,
 15 “arylalkoxy”, or “aryloxyalkyl”, means a 6-14 membered carbocyclic aromatic monocyclic or polycyclic ring system, preferably a 5-8 membered ring system. Examples include phenyl, naphthyl, anthracenyl, 1,2-dihydronaphthyl, 1,2,3,4-tetrahydronaphthyl, fluorenyl, indanyl, indenyl and the like. The term “aryl” also includes fused aryl groups, wherein a monocyclic aryl rings, for example phenyl, is
 20 fused to a cycloalkyl, an aromatic ring, or both, or a combination thereof. Specifically, fused aryl groups include up to three rings, or more specifically, two rings fused together. The term “aryl” may be used interchangeably with the terms “aromatic group”, “aryl ring” “aromatic ring”, “aryl group” and “aromatic group.” Unless otherwise described, exemplary substituents for a substituted aryl group
 25 include groups represented by R⁵.

“Aroyl” means an aryl or an arylalkyl attached through a $-\text{C}(\text{O})-$ group. Aroyl includes includes, but is not limited to, phenoyl and benzoyl.

The term “aryloxy” means an aryl moiety attached through an oxygen linking atom. Aryloxy includes, but not limited to, phenoxy, benzoxy, or pyridinyloxy.

The term “cycloalkyl”, used alone or as part of a larger moiety, means a
5 monocyclic, bicyclic or tricyclic, saturated hydrocarbon ring having 3-10 carbon atoms, preferably 3-7 carbon atoms, and includes, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[2.2.2]octyl, bicyclo[2.2.1]heptyl, spiro [4.4]nonane, adamantyl and the like. The term “cycloalkyl” also includes fused cycloalkyl groups, wherein a cycloalkyl ring is
10 fused to non-aromatic cycloalkyl ring, to a heterocyclyl group, to a heteroaryl group, to an aryl ring, or to any combination thereof. Specifically, fused cycloalkyl groups include up to three rings, or more specifically, two rings fused together. Unless otherwise described, exemplary substituents for a substituted cycloalkyl group include groups represented by R⁵.

15 The term “cycloalkoxy” means a cycloalkyl radical attached through an oxygen linking atom. “(C₃-C₆)cycloalkoxy” includes cyclopropyloxy, cyclobutyloxy, cyclopentyloxy and cyclohexyloxy.

“Hetero” refers to the replacement of at least one carbon atom member in a ring system with at least one heteroatom selected from N, S, and O or combinations
20 thereof. When one heteroatom is S, it can be optionally mono- or di-oxygenated (*i.e.*, -S(O)-, -S(O)₂-). A hetero ring may have 1, 2, 3, or 4 carbon atom members replaced by a heteroatom.

“Heteroaryl”, used alone or as part of a larger moiety as in “heteroarylalkyl” or “heteroarylalkoxy”, means a 5-10 membered, preferably 5-7 membered,
25 monovalent heteroaromatic monocyclic and polycyclic ring radical containing 1 to 4 heteroatoms independently selected from N, O, and S. The term “heteroaryl” also includes fused heteroaryl groups, wherein a monocyclic heteroaryl ring is fused to non-aromatic cycloalkyl ring, to a heterocyclyl group, to a heteroaryl group, to an aryl ring, or to any combination thereof. Specifically, fused heteroaryl groups
30 include up to three rings, or more specifically, two rings fused together. Heteroaryl groups include, but are not limited to, furyl, thienyl, thiophenyl, thiophene, pyrrolyl,

oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, pyridinyl, pyridinyl-N-oxide, pyridazinyl, pyrimidinyl, pyrazinyl, indoliziny, indolyl, isoindolyl, imidazo[4,5-b]pyridine, benzo[b]furyl, benzo[b]thienyl, indazolyl, benzimidazolyl, benzthiazolyl, purinyl, 4H-quinoliziny, quinoliny, isoquinoliny, quinazoliny, benzothienyl, benzofuranyl, 2,3-dihydrobenzofuranyl, benzodioxolyl, benzimidazolyl, indazolyl, benzisoxazolyl, benzoxazolyl, benzothiazolyl, cinnoliny, phthalziny, quinazoliny, quinoxaliny, 1,8-naphthyridiny, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,3,4-oxadiazolyl, 1,2,5-thiadiazolyl, 1,2,5-thiadiazolyl-1-oxide, 1,2,5-thiadiazolyl-1,1-dioxide, 1,3,4-thiadiazolyl, 1,2,4-triaziny, 1,3,5-triaziny, tetrazolyl, and pteridinyl. The terms “heteroaryl”, “heteroaromatic”, “heteroaryl ring”, “heteroaryl group” and “heteroaromatic group” are used interchangeably herein. “Heteroarylalkyl” means alkyl substituted with heteroaryl; and “heteroarylalkoxy” means alkoxy substituted with heteroaryl. Unless otherwise described, exemplary substituents for a substituted heteroaryl group include the include groups represented by R⁵.

The term “heteroaryloxy” means a heteroaryl or heteroaryl(C₁-C₃)alkyl moiety attached through an oxygen linking atom. Heteroaryloxy includes, but is not limited to, pyridinyloxy.

The term “heterocyclyl” means a 4-, 5-, 6- or 7-membered saturated or partially unsaturated heterocyclic ring containing 1 to 4 heteroatoms independently selected from N, O, and S or a combination thereof. The term “heterocyclyl” also includes fused heterocyclyl groups, wherein a monocyclic heterocyclyl ring is fused to non-aromatic cycloalkyl ring, to a heterocyclyl group, to an aryl ring, or to any combination thereof. Specifically, fused heterocyclyl groups include up to three rings, or more specifically, two rings fused together. Exemplary heterocyclyls include azetidine, pyrrolidine, pyrrolidin-2-one, 1-methylpyrrolidin-2-one, piperidine, piperidin-2-one, 2-pyridone, 4-pyridone, piperazine, 1-(2,2,2-trifluoroethyl)piperazine, piperazin-2-one, 5,6-dihydropyrimidin-4-one, pyrimidin-4-one, tetrahydrofuran, tetrahydropyran, tetrahydrothiophene, tetrahydrothiopyran, isoxazolidine, 1,3-dioxolane, 1,3-dithiolane, 1,3-dioxane, 1,4-dioxane, 1,3-dithiane, 1,4-dithiane, oxazolidin-2-one, imidazolidin-2-one, imidazolidine-2,4-dione,

tetrahydropyrimidin-2(1H)-one, morpholine, N-methylmorpholine, morpholin-3-one, 1,3-oxazinan-2-one, thiomorpholine, thiomorpholine 1,1-dioxide, tetrahydro-1,2,5-thiaoxazole 1,1-dioxide, tetrahydro-2H-1,2-thiazine 1,1-dioxide, hexahydro-1,2,6-thiadiazine 1,1-dioxide, tetrahydro-1,2,5-thiadiazole 1,1-dioxide and
5 isothiazolidine 1,1-dioxide. Unless otherwise described, exemplary substituents for a substituted heterocyclyl group include groups represented by R⁵.

The term "heterocyclyloxy" means a heterocyclyl radical attached through an oxygen linking atom. "Heterocyclyloxy" includes, but is not limited to, glucosyloxy.

10 A spiro cycloalkyl has two rings which have only one ring atom in common. The first ring is a monocyclic cycloalkyl and the second ring is a monocyclic cycloalkyl. Example of a spiro cycloalkyl includes, but is not limited to, spiro[4.4]nonane, spiro[4.5]decane, and spiro[5.5]undecane. Unless otherwise described, exemplary substituents for a substituted spiro cycloalkyl group include
15 groups represented by R⁵.

A spiro heterocyclyl has two rings which have only one ring atom in common. The first ring is a monocyclic heterocyclyl and the second ring is a monocyclic cycloalkyl or a monocyclic heterocyclyl. For example, the second ring is a (C₃-C₆)cycloalkyl. Alternatively, the second ring is phenyl. Example of a spiro
20 heterocyclyl includes, but are not limited to, azaspiro[4.4]nonane, 7-azaspiro[4.4]nonane, azaspiro[4.5]decane, 8-azaspiro[4.5]decane, azaspiro[5.5]undecane, 3-azaspiro[5.5]undecane and 3,9-diazaspiro[5.5]undecane. Unless otherwise described, exemplary substituents for a substituted spiro heterocyclyl group include groups represented by R⁵.

25 The terms "halogen" and "halo" are interchangeably used herein and each refers to fluorine, chlorine, bromine, or iodine.

Certain of the disclosed compounds may exist in various stereoisomeric forms. Stereoisomers are compounds that differ only in their spatial arrangement. Enantiomers are pairs of stereoisomers whose mirror images are not superimposable,
30 most commonly because they contain an asymmetrically substituted carbon atom that acts as a chiral center. "Enantiomer" means one of a pair of molecules that are

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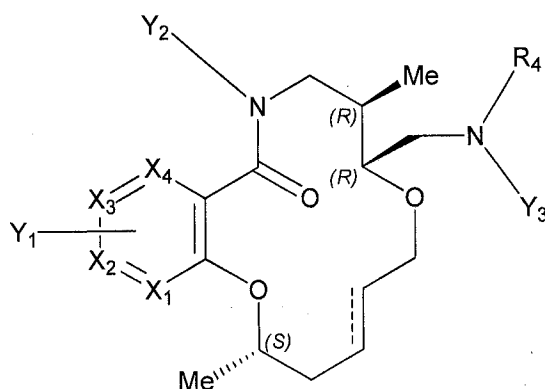
mirror images of each other and are not superimposable. Diastereomers are stereoisomers that are not related as mirror images, most commonly because they contain two or more asymmetrically substituted carbon atoms. “R” and “S” represent the configuration of substituents around one or more chiral carbon atoms.

- 5 Enantiomers of a compound can be prepared, for example, by separating an enantiomer from a racemate using one or more well-known techniques and methods, such as, for example, chiral chromatography and separation methods based thereon. The appropriate technique and/or method for separating an enantiomer of a compound described herein from a racemic mixture can be readily determined by
10 those of skill in the art.

“Racemate” or “racemic mixture” means a compound containing two enantiomers, wherein such mixtures exhibit no optical activity; i.e., they do not rotate the plane of polarized light.

- “Geometric isomer” means isomers that differ in the orientation of
15 substituent atoms in relationship to a carbon-carbon double bond, to a cycloalkyl ring, or to a bridged bicyclic system. Atoms (other than H) on each side of a carbon-carbon double bond may be in an E (substituents are on opposite sides of the carbon-carbon double bond) or Z (substituents are oriented on the same side) configuration.

- “R,” “S,” “S*,” “R*,” “E,” “Z,” “cis,” and “trans,” indicate configurations
20 relative to the core molecule. For example, a specific stereochemical designation of a macrolactam compound of the invention, or a pharmaceutically acceptable salt thereof, is as follows:



Certain of the disclosed compounds may exist in atropisomeric forms.

- 25 Atropisomers are stereoisomers resulting from hindered rotation about single bonds

where the steric strain barrier to rotation is high enough to allow for the isolation of the conformers.

The compounds of the invention may be prepared as individual isomers by either isomer-specific synthesis or resolved from an isomeric mixture. Conventional
5 resolution techniques include forming the salt of a free base of each isomer of an isomeric pair using an optically active acid (followed by fractional crystallization and regeneration of the free base), forming the salt of the acid form of each isomer of an isomeric pair using an optically active amine (followed by fractional
10 crystallization and regeneration of the free acid), forming an ester or amide of each of the isomers of an isomeric pair using an optically pure acid, amine or alcohol (followed by chromatographic separation and removal of the chiral auxiliary), or resolving an isomeric mixture of either a starting material or a final product using various well known chromatographic methods.

When the stereochemistry of a disclosed compound is named or depicted by
15 structure, the named or depicted stereoisomer is at least 60%, 70%, 80%, 90%, 99% or 99.9% by weight relative to the other stereoisomers. When a single enantiomer is named or depicted by structure, the depicted or named enantiomer is at least 60%, 70%, 80%, 90%, 99% or 99.9% by weight optically pure. When a single diastereomer is named or depicted by structure, the depicted or named diastereomer
20 is at least 60%, 70%, 80%, 90%, 99% or 99.9% by weight pure. Percent optical purity is the ratio of the weight of the enantiomer or over the weight of the enantiomer plus the weight of its optical isomer. Diastereomeric purity by weight is the ratio of the weight of one diastereomer or over the weight of all the diastereomers.

25 When the stereochemistry of a disclosed compound is named or depicted by structure, the named or depicted stereoisomer is at least 60%, 70%, 80%, 90%, 99% or 99.9% by mole fraction pure relative to the other stereoisomers. When a single enantiomer is named or depicted by structure, the depicted or named enantiomer is at least 60%, 70%, 80%, 90%, 99% or 99.9% by mole fraction pure. When a single
30 diastereomer is named or depicted by structure, the depicted or named diastereomer is at least 60%, 70%, 80%, 90%, 99% or 99.9% by mole fraction pure. Percent

purity by mole fraction is the ratio of the moles of the enantiomer or over the moles of the enantiomer plus the moles of its optical isomer. Similarly, percent purity by moles fraction is the ratio of the moles of the diastereomer or over the moles of the diastereomer plus the moles of its isomer

5 When a disclosed compound is named or depicted by structure without indicating the stereochemistry, and the compound has at least one chiral center, it is to be understood that the name or structure encompasses either enantiomer of the compound free from the corresponding optical isomer, a racemic mixture of the compound or mixtures enriched in one enantiomer relative to its corresponding
10 optical isomer.

 When a disclosed compound is named or depicted by structure without indicating the stereochemistry and has two or more chiral centers, it is to be understood that the name or structure encompasses a diastereomer free of other diastereomers, a number of diastereomers free from other diastereomeric pairs,
15 mixtures of diastereomers, mixtures of diastereomeric pairs, mixtures of diastereomers in which one diastereomer is enriched relative to the other diastereomer(s) or mixtures of diastereomers in which one or more diastereomer is enriched relative to the other diastereomers.

 As used herein, "substantially pure" means that the depicted or named
20 compound is at least about 60% by weight. For example, "substantially pure" can mean about 60%, 70%, 72%, 75%, 77%, 80%, 82%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.9%, or a percentage between 70% and 100%. In one embodiment, substantially pure means that the depicted or named compound is at least about 75% pure. In a specific
25 embodiment, substantially pure means that the depicted or named compound is at least about 90 % by weight.

 As used herein the terms "subject" and "patient" may be used interchangeably, and means a mammal in need of treatment, e.g., companion animals (e.g., dogs, cats, and the like), farm animals (e.g., cows, pigs, horses, sheep,
30 goats and the like) and laboratory animals (e.g., rats, mice, guinea pigs and the like). Typically, the subject is a human in need of treatment.

- 40 -

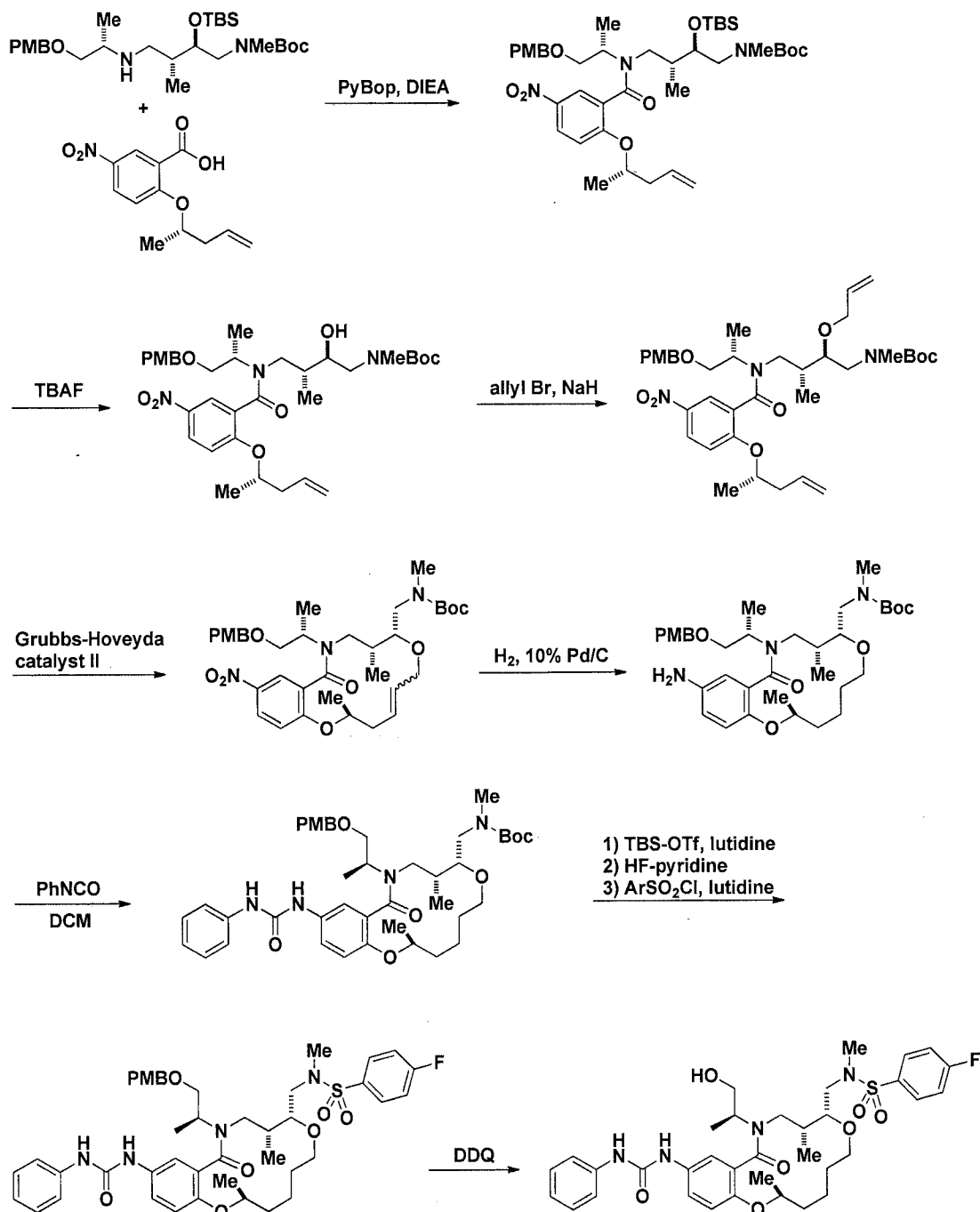
Malaria is a parasitic infection of red blood cells caused by eukaryotic protists of the genus *Plasmodium* in the phylum Apicomplexa. Human malaria is known to be caused by five different *Plasmodium* species: *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*, *Plasmodium malariae* or *Plasmodium knowlesi*. Malaria parasites are transmitted by female *Anopheles* mosquitoes. The parasites multiply within red blood cells, causing symptoms that include symptoms of anemia (light headedness, shortness of breath, tachycardia), as well as other general symptoms such as an enlarged spleen, fatigue, fever, chills, nausea, flu-like illness, and in severe cases, coma and death. The methods described herein are useful for treating human malaria caused by a *Plasmodium* species, such as *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*, *Plasmodium malariae* or *Plasmodium knowlesi*. In a particular embodiment, the invention relates to a method of treating a malaria caused by *Plasmodium falciparum*. Both drug-resistant and drug-sensitive strains of *Plasmodium* are intended to be included herein.

EXEMPLIFICATION

General synthetic scheme:

20

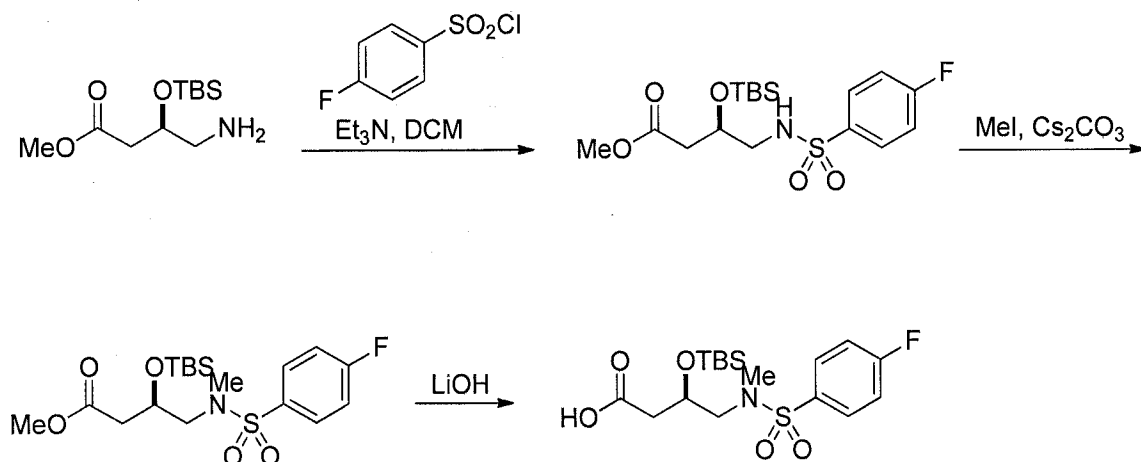
- 41 -



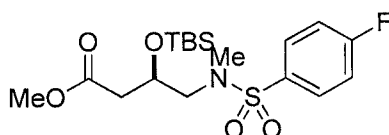
For the following synthetic routes, intermediates and final compounds were synthesized using the procedures previously reported in Marcaurelle, L. A.; Comer, E.; Dandapani, S.; Duvall, J. R.; Gerard, B.; Kesavan, S.; Lee, M. D, IV; Liu, H.; Lowe, J. T.; Marie, J.-C.; Mulrooney, C. A.; Pandya, B. A.; Rowley, A.; Ryba, T. D.; Suh, B.-C.; Wei, J.; Young, D. W.; Akella, L. B.; Ross, N. B.; Zhang, Y.-L.; Fass, D. M.; Reis, S. A.; Zhao, W.-N.; Haggarty, S. J.; Palmer, M.; Foley, M. A. *J. Am. Chem. Soc.* **2010**, *132*, 16962-16976.

10 Des-Methyl Acid synthesis:

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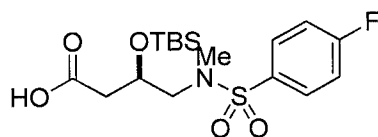
Intermediate A:



5 **(R)-methyl 3-((tert-butyldimethylsilyl)oxy)-4-(4-fluoro-N-methylphenylsulfonamido)butanoate**

To a solution of (R)-methyl 4-amino-3-((tert-butyldimethylsilyl)oxy)butanoate (500 mg, 2.02 mmol) in CH₂Cl₂ (20 mL) was added 4-fluorobenzenesulfonyl chloride (590 mg, 3.03 mmol) and triethylamine (1.4 mL, 10 mmol). The reaction mixture was stirred at rt for 16 h, then diluted with H₂O and CH₂Cl₂. The phases were partitioned and the organic layer dried (MgSO₄) and solvent evaporated. The residue was purified with SiO₂ chromatography to yield 400 mg (49%) of product with some impurities. This product ((R)-methyl 3-((tert-butyldimethylsilyl)oxy)-4-(4-fluorophenylsulfonamido)butanoate) was carried on to the next step without further purification. To a solution of (R)-methyl 3-((tert-butyldimethylsilyl)oxy)-4-(4-fluorophenylsulfonamido)butanoate (433 mg, 1.07 mmol) in DMF (11 mL) was added CsCO₃ (696 mg, 2.14 mmol) and iodomethane (0.080 mL, 1.28 mmol). The reaction mixture was stirred overnight at rt, then diluted with EtOAc and H₂O. The phases were partitioned and the organic layer dried (MgSO₄) and solvent evaporated. The residue was purified with SiO₂ chromatography to yield 300 mg (67%) of product. ¹H NMR (300 MHz, CDCl₃) δ 7.83 – 7.73 (m, 2H), 7.25 – 7.14 (m, 2H), 4.38 – 4.27 (m, 1H), 3.67 (s, 3H), 3.07 – 2.94 (m, 3H), 2.81 (s, 3H), 2.71 (dd, *J* = 15.4, 5.6 Hz, 1H), 2.51 (dd, *J* = 15.5, 6.5 Hz, 2H), 0.86 (s, 9H), 0.07 – 0.01 (m, 6H). MS calculated for C₁₈H₃₁FNO₅SSi [M+H]⁺: 420. Found: 420.

Intermediate B:

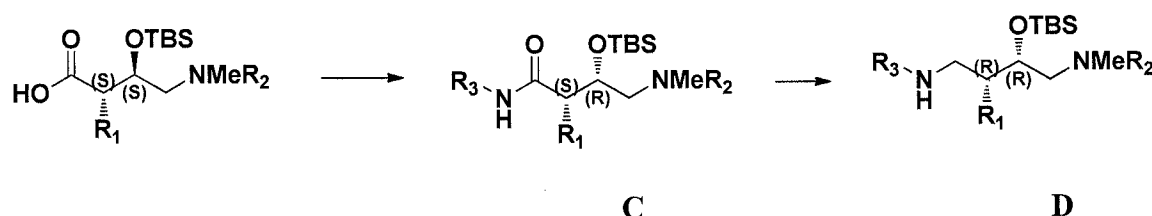


30 **(R)-3-((tert-butyldimethylsilyl)oxy)-4-(4-fluoro-N-methylphenylsulfonamido)butanoic acid**

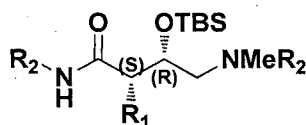
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To a chilled (ice-H₂O bath) solution of (*R*)-methyl 3-((*tert*-butyldimethylsilyl)oxy)-4-(4-fluoro-*N*-methylphenylsulfonamido)butanoate (1.00 g, 2.38 mmol) in THF (19 mL) and H₂O (4.8 mL) was added LiOH (150 mg, 3.57 mmol). The reaction mixture was allowed to warm to rt and stirred overnight. The mixture was concentrated to remove organic solvent, then acidified with 1N HCl and the aqueous phase extracted with EtOAc. The phases were separated and the organic layer dried over MgSO₄ and solvent evaporated. The crude material was carried on to the next step without further purification. ¹H NMR (300 MHz, CDCl₃) δ 7.82 – 7.72 (m, 2H), 7.26 – 7.16 (m, 2H), 4.40 – 4.29 (m, 1H), 3.03 (qd, *J* = 13.9, 5.6 Hz, 2H), 2.82 (s, 3H), 2.81 – 2.73 (m, 1H), 2.57 (dd, *J* = 15.8, 6.5 Hz, 1H), 0.87 (s, 9H), 0.09 (s, 6H). MS calculated for C₁₇H₂₉FNO₅SSi [M+H]⁺: 406. Found: 406.

Synthesis of linear amine intermediate D:



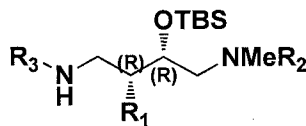
Intermediate C:



No.	Structure	Name	MS
C1		tert-butyl ((2R,3S)-2-((tert-butyldimethylsilyl)oxy)-3-methyl-4-(methoxycarbonyl)butyl)carbamate	[M+H] ⁺ calcd 375; found, 375
C2		tert-butyl ((2R,3S)-2-((tert-butyldimethylsilyl)oxy)-3-isopropyl-4-(methoxycarbonyl)butyl)carbamate	[M+H] ⁺ calcd 403; found, 403
C3		tert-butyl ((2R,3S)-2-((tert-butyldimethylsilyl)oxy)-4-((2-((4-methoxybenzyl)oxy)ethyl)amino)-3-methyl-4-(methoxycarbonyl)butyl)carbamate	[M+H] ⁺ calcd 525; found, 525
C4		tert-butyl ((2R,3S)-4-(((S)-1-(tert-butoxy)propan-2-yl)amino)-2-((tert-butyldimethylsilyl)oxy)-3-methyl-4-(methoxycarbonyl)butyl)carbamate	[M+H] ⁺ calcd 475; found, 475

No.	Structure	Name	MS
C5		tert-butyl ((2R,3S)-2-((tert-butyldimethylsilyl)oxy)-4-(((R)-1-((4-methoxybenzyl)oxy)propan-2-yl)amino)-3-methyl-4-oxobutyl)(methyl)carbamate	[M+H] ⁺ calcd 539; found, 539
C6		tert-butyl ((2R,3S)-2-((tert-butyldimethylsilyl)oxy)-4-(((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)amino)-3-methyl-4-oxobutyl)(methyl)carbamate	[M+H] ⁺ calcd 539; found, 539
C7		(R)-3-((tert-butyldimethylsilyl)oxy)-4-(4-fluoro-N-methylphenylsulfonamido)-N-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)butanamide	[M+H] ⁺ calcd 583; found 583,
C8		(R)-tert-butyl 5-((S)-1-(((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)amino)-1-oxopropan-2-yl)-2,2-dimethyloxazolidine-3-carboxylate	[M+H] ⁺ calcd 451; found 451,

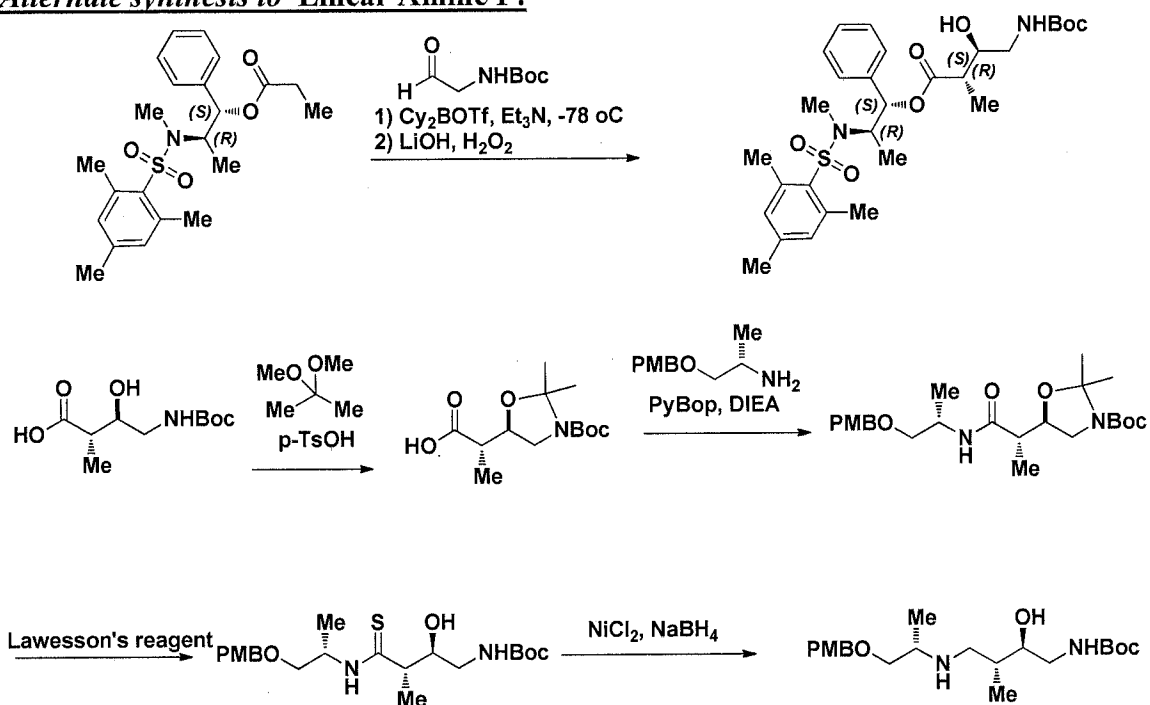
Intermediate D:



#	Structure	Name	MS
D 1		tert-butyl ((2R,3R)-2-((tert-butyldimethylsilyl)oxy)-3-methyl-4-(methylamino)butyl)(methyl)carbamate	[M+H] ⁺ calcd 361; found, 361
D 2		tert-butyl ((2R,3R)-2-((tert-butyldimethylsilyl)oxy)-4-(isopropylamino)-3-methylbutyl)(methyl)carbamate	[M+H] ⁺ calcd 389; found, 389
D 3		tert-butyl ((2R,3R)-2-((tert-butyldimethylsilyl)oxy)-4-((2-((4-methoxybenzyl)oxy)ethyl)amino)-3-methylbutyl)(methyl)carbamate	[M+H] ⁺ calcd 511; found, 511
D 4		tert-butyl ((2R,3R)-4-(((S)-1-(tert-butoxy)propan-2-yl)amino)-2-((tert-butyldimethylsilyl)oxy)-3-methylbutyl)(methyl)carbamate	[M+H] ⁺ calcd 461; found, 461

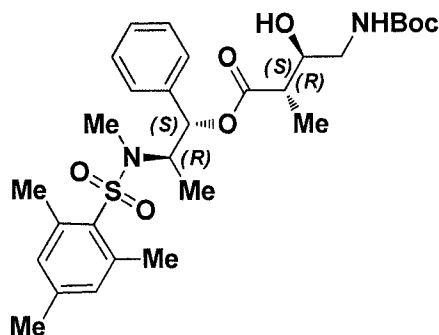
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D 5		tert-butyl ((2R,3R)-2-((tert-butyldimethylsilyl)oxy)-4-(((R)-1-((4-methoxybenzyl)oxy)propan-2-yl)amino)-3-methylbutyl)(methyl)carbamate	[M+H] ⁺ calcd 525; found, 525
D 6		tert-butyl ((2R,3R)-2-((tert-butyldimethylsilyl)oxy)-4-(((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)amino)-3-methylbutyl)(methyl)carbamate	[M+H] ⁺ calcd 525; found, 525
D 7		N-((R)-2-((tert-butyldimethylsilyl)oxy)-4-(((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)amino)butyl)-4-fluoro-N-methylbenzenesulfonamide	[M+H] ⁺ calcd 569; found 569,

Alternate synthesis to Linear Amine I:



5 Intermediate E:

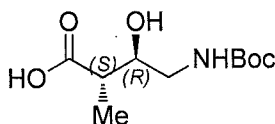
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(2*S*,3*R*)-(1*S*,2*R*)-1-phenyl-2-(*N*,2,4,6-tetramethylphenylsulfonamido)propyl 4-((*tert*-butoxycarbonyl)amino)-3-hydroxy-2-methylbutanoate

5 A flame dried 3-neck flask equipped with an internal temperature probe and a dropping funnel was charged with a solution of (1*S*,2*R*)-1-phenyl-2-(*N*,2,4,6-tetramethylphenylsulfonamido)propyl propionate (12.0 g, 29.7 mmol) in dry CH₂Cl₂ (102 mL) under N₂. The solution was chilled to -72 °C and Et₃N (12.4 mL, 89.0 mmol) was added dropwise. A solution of dicyclohexylboron triflate (19.4 g, 59.5 mmol) in dry CH₂Cl₂ (64 mL) was then added dropwise to the reaction mixture, maintaining internal temperature below -67 °C. Stirring was continued for 2 h keeping the reaction temperature at -72 °C, then a solution of *tert*-butyl (2-oxoethyl)carbamate (9.47 g, 59.5 mmol) in dry CH₂Cl₂ (32 mL) was added dropwise, maintaining the reaction temperature below -70 °C. Stirring was continued for 2 h keeping the reaction temperature at -72 °C, then the reaction was allowed to warm to 0 °C and stirring continued for 1 h. The reaction was quenched with a solution of MeOH (120 mL) and pH 7 buffer (12 mL) added dropwise, then a solution of H₂O₂ (16.7 mL, 30% in H₂O, 164 mmol) was added dropwise, maintaining reaction temperature below 23 °C. The mixture was stirred overnight at rt. The mixture was concentrated under reduced pressure to remove the MeOH, then partitioned between CH₂Cl₂ and H₂O. The aqueous phase was washed with CH₂Cl₂, and the combined organic layers were washed with H₂O, dried over Na₂SO₄, and the solvent evaporated. Purification was accomplished via SiO₂ chromatography to yield 14.8 g (89%) of desired product. ¹H NMR (300 MHz, CDCl₃) δ 7.23 – 7.14 (m, 3H), 7.08 – 6.99 (m, 2H), 6.86 (s, 2H), 5.77 (d, *J* = 5.2 Hz, 1H), 5.07 (br s, 1H), 4.10 – 3.98 (m, 1H), 3.82-3.71 (m, 1H), 3.44 – 3.25 (m, 2H), 3.17-3.03 (m, 1H), 2.71 (s, 3H), 2.69-2.56 (m, 1H), 2.41 (s, 6H), 2.28 (s, 3H), 1.41 (s, 9H), 1.29 – 1.24 (m, 3H), 1.16 (d, *J* = 7.2 Hz, 3H). MS calculated for C₂₉H₄₂N₂O₇S [M+H]⁺: 563. Found: 563.

Intermediate F:

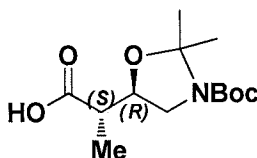


(2*S*,3*R*)-4-((*tert*-butoxycarbonyl)amino)-3-hydroxy-2-methylbutanoic acid

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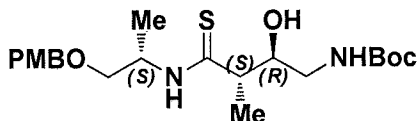
To a chilled (ice-H₂O bath) solution of (2*S*,3*R*)-(1*S*,2*R*)-1-phenyl-2-(*N*,2,4,6-tetramethylphenylsulfonamido)propyl 4-((*tert*-butoxycarbonyl)amino)-3-hydroxy-2-methylbutanoate (14.7 g, 26.1 mmol) in MeOH (131 mL) and *t*-BuOH (131 mL) was added a solution of H₂O₂ (16.0 mL, 30%, 157 mmol) in H₂O followed by a solution of NaOH (78 mL, 1*N*, 78 mmol) in H₂O while maintaining the internal temperature of the reaction mixture below 8 °C. The mixture was stirred overnight allowing to warm to rt. The mixture was concentrated under reduced pressure to remove the MeOH, then partitioned between EtOAc and H₂O. The organic layer was washed with H₂O, then the combined aqueous phase was washed with EtOAc. The aqueous layer was then acidified to pH 3 with 6*N* HCl, then extracted with EtOAc. The second organic layer was washed with H₂O, dried over Na₂SO₄, and the solvent evaporated to yield 5.51 g (90%) of pure product. ¹H NMR (300 MHz, CDCl₃) δ 9.21 (br s, 1H), 5.20 (br s, 1H), 4.00 – 3.75 (m, 1H), 3.44-3.27 (m, 1H), 3.25 – 3.10 (m, 1H), 2.63 – 2.52 (m, 1H), 1.43 (s, 9H), 1.25 (d, *J* = 10.3 Hz, 3H). MS calculated for C₁₀H₂₀NO₅ [M-H]⁺: 232. Found: 232.

Intermediate G:

**(*S*)-2-((*R*)-3-(*tert*-butoxycarbonyl)-2,2-dimethyloxazolidin-5-yl)propanoic acid**

To a solution of (2*S*,3*R*)-4-((*tert*-butoxycarbonyl)amino)-3-hydroxy-2-methylbutanoic acid (5.51 g, 23.6 mmol) in acetone (118 mL) was added 2,2-dimethoxypropane (59 mL, 470 mmol) followed by *p*-toluenesulfonic acid hydrate (449 mg, 2.36 mmol). The reaction mixture was stirred for 30 min, then diluted with H₂O and concentrated under reduced pressure to remove the organics. The aqueous phase was then extracted with CH₂Cl₂, the organic phase washed with H₂O, dried over Na₂SO₄, and the solvent evaporated to yield 5.28 g (82%) of pure product. ¹H NMR (300 MHz, CDCl₃) δ 9.21 (br s, 1H), 4.27 (dt, *J* = 14.2, 7.2 Hz, 1H), 3.81 – 3.56 (m, 1H), 3.25 – 3.09 (m, 1H), 2.67 (br s, 1H), 1.55 (br s, 3H), 1.46 (s, 9H), 1.21 – 1.13 (m, 3H). MS calculated for C₁₃H₂₄NO₅ [M-H]⁺: 272. Found: 272.

Intermediate H:

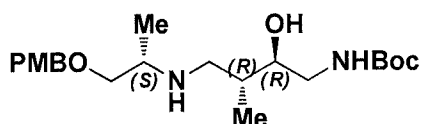
***tert*-butyl ((2*R*,3*S*)-2-hydroxy-4-(((*S*)-1-((4-methoxybenzyl)oxy)propan-2-yl)amino)-3-methyl-4-thioxobutyl)carbamate**

To a solution of (*S*)-2-((*R*)-3-(*tert*-butoxycarbonyl)-2,2-dimethyloxazolidin-5-yl)propanoic acid (5.20 g, 11.5 mmol) in dry toluene (115 mL) was added

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Lawesson's reagent (2.57 g, 6.35 mmol). The reaction mixture was stirred under N₂ while heated in a 42 °C oil bath for 6 h, then cooled, and absorbed onto SiO₂ and purified via SiO₂ chromatography to yield 2 products: 2.04 g (41%) of *tert*-butyl ((2*R*,3*S*)-2-hydroxy-4-(((*S*)-1-((4-methoxybenzyl)oxy)propan-2-yl)amino)-3-methyl-4-thioxobutyl)carbamate and 1.91 g (36%) of (*R*)-*tert*-butyl 5-(((*S*)-1-(((*S*)-1-((4-methoxybenzyl)oxy)propan-2-yl)amino)-1-thioxopropan-2-yl)-2,2-dimethyloxazolidine-3-carboxylate (desired product). ¹H NMR (300 MHz, CDCl₃) δ 8.50-8.39 (m, 1H), 7.25 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 5.13-5.00 (m, 1H), 4.88 – 4.73 (m, 1H), 4.47 (q, *J* = 11.6 Hz, 2H), 4.11 – 4.01 (m, 1H), 3.79 (s, 3H), 3.78 – 3.68 (m, 1H), 3.63-3.44 (m, 2H), 3.38-3.23 (m, 2H), 3.13-3.01 (m, 2H), 2.79-2.70 (m, 1H), 1.43 (s, 9H), 1.35 – 0.88 (m, 6H). MS calculated for C₂₁H₃₄N₂O₅S [M+H]⁺: 427. Found: 427.

Linear Amine Intermediate I:

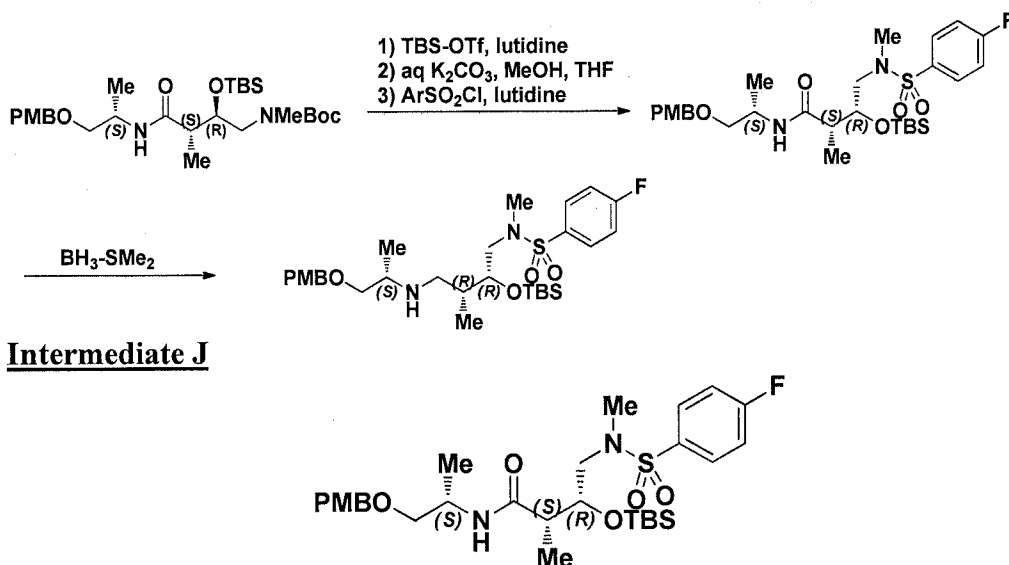


tert-butyl ((2*R*,3*R*)-2-hydroxy-4-(((*S*)-1-((4-methoxybenzyl)oxy)propan-2-yl)amino)-3-methylbutyl)carbamate

To a solution of (*R*)-*tert*-butyl 5-(((*S*)-1-(((*S*)-1-((4-methoxybenzyl)oxy)propan-2-yl)amino)-1-thioxopropan-2-yl)-2,2-dimethyloxazolidine-3-carboxylate (1.17 g, 2.74 mmol) in THF (34 mL) and MeOH (34 mL) was added nickel(II) chloride (3.02 g, 23.3 mmol). The yellow suspension was chilled in an ice-H₂O bath, and NaBH₄ (5.19 g, 137 mmol) was added in portions slowly. Vigorous bubbling was observed throughout addition. The black mixture was stirred in the ice bath until the bubbling subsided, then the bath was removed and the mixture stirred at ambient temperature for 2 h. Diethylenetriamine (25 mL, 233 mmol) was then added to the mixture and stirred for 30 min. The reaction mixture was concentrated under reduced pressure to remove the volatile organic solvents, then the residue was partitioned between EtOAc and H₂O in a separatory funnel. An additional 25 mL of diethylenetriamine was added, and the funnel vigorously shaken until the aqueous turned from black to purple. The phases were separated and the aqueous phase extracted with additional EtOAc. The combined organic phases were washed with brine, dried (Na₂SO₄) and the solvent evaporated to yield 0.93 g (86%) of pure product. ¹H NMR (300 MHz, CDCl₃) δ 7.24 (d, *J* = 9.7 Hz, 3H), 6.93 – 6.82 (m, 2H), 5.07 (br s, 1H), 4.42 (s, 2H), 3.79 (s, 3H), 3.57 – 3.47 (m, 1H), 3.41-3.27 (m, 2H), 3.10-2.99 (m, 1H), 2.93-2.74 (m, 2H), 2.55 (dd, *J* = 12.1, 10.2 Hz, 1H), 1.67-1.53 (m, 1H), 1.44 (s, 9H), 1.06 (d, *J* = 8.6 Hz, 3H), 1.01 – 0.74 (m, 3H). MS calculated for C₂₁H₃₇N₂O₅ [M+H]⁺: 397. Found: 397.

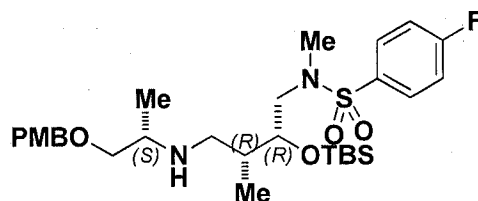
Synthesis of Linear amine intermediate K

- 49 -



5 **(2S,3R)-3-((tert-butyldimethylsilyl)oxy)-4-(4-fluoro-N-methylphenylsulfonamido)-N-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2-methylbutanamide**

A solution of C6 (20.0g, 37.1mmol, 1.0 eqv) in DCM (742mL, 0.05 M) under N₂ was cooled to 0°C and treated with 2,6-lutidine (21.62mL, 186 mmol, 5 eqv) and tert-butyldimethylsilyl trifluoromethanesulfonate (21.90mL, 93mmol, 2.5eqv). The reaction was stirred at 0°C for 25 min and then at RT for 3.5h at which point the reaction was treated with 2,6-lutidine (21.62mL, 186 mmol, 5 eqv) before being quenched with 500mL saturated ammonium chloride. The crude product was extracted with 2 x 500mL DCM, washed with 300mL H₂O, and dried with Na₂SO₄. The solvent was evaporated under reduced pressure and the crude material diluted with MeOH, THF and treated with a 100mg/mL aqueous solution of potassium bicarbonate in a 3:1:1 ratio respectively (111mL:37.1mL:37.1mL, 0.2M). The mixture was stirred at rt for 3h and then concentrated under reduced pressure. The residue was diluted with 50mL H₂O, 5mL saturated sodium bicarbonate, and 10mL brine and the crude product was extracted 3 x 100mL DCM, dried with MgSO₄ and concentrated under reduced pressure. The crude material was dissolved in DCM (371mL, 0.1 M) and treated with 2,6-lutidine (8.64mL, 74.2mmol, 2 eqv) followed by 4-fluorobenzene-1-sulfonyl chloride (10.83g, 55.7mmol, 1.5 eqv) and stirred at rt for 18h. The reaction was diluted with H₂O and the crude product was extracted 2 x 200 mL DCM, washed 3 x 200mL H₂O, dried with NaSO₄ and concentrated under reduced pressure. This material was chromatographed on silica, eluting with 10-50% ethyl acetate in hexanes to afford 20.8g (94% yield) of the desired product as a clear light yellow oil. ¹H NMR (300 MHz, CDCl₃) δ 7.76 (m, 2H), 7.2 (m, 4H), 6.86 (m, 2H), 4.42 (m, 2H), 4.15(m, 1H), 4.03 (m, 1H), 3.79 (d, *J* = 4.4 Hz, 3H), 3.36 (m, 2H), 3.10 (dt, *J* = 16.0, 8.0 Hz, 1H), 2.76 (m, 4H), 2.60 (qd, *J* = 7.2, 3.1 Hz, 1H), 1.25 (dd, *J* = 11.5, 5.8 Hz, 3H), 1.13 (t, *J* = 7.8 Hz, 3H), 0.90 (d, *J* = 4.8 Hz, 9H), 0.19 (s, 3H), 0.12 (m, 3H). MS (ESI) calcd for C₂₉H₄₅FN₂O₆SSi [M + H]⁺: 597. Found: 597

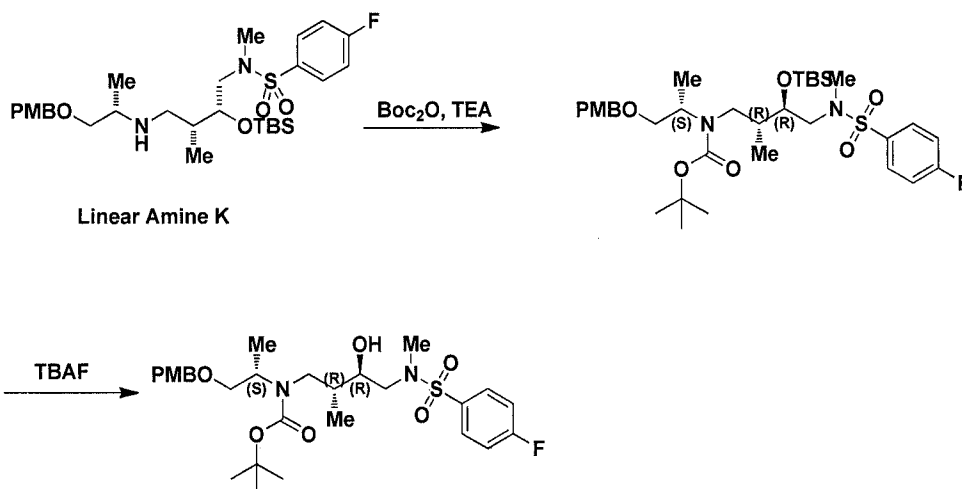
Linear amine Intermediate K

N-((2R,3R)-2-((tert-butyldimethylsilyl)oxy)-4-(((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)amino)-3-methylbutyl)-4-fluoro-N-methylbenzenesulfonamide

A solution of (2S,3R)-3-((tert-butyldimethylsilyl)oxy)-4-(4-fluoro-N-methylphenylsulfonamido)-N-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2-methylbutanamide (20.8g, 34.9mmol, 1.0 eqv) was dissolved in THF (349mL, 0.1M) under N₂ and cooled to 0°C. Borane-methyl sulfide complex (13.24mL, 139mmol, 4eqv) was added dropwise. The solution was left to stir at 0°C until no bubbling was observed at which time it was warmed to rt and stirred for 15 min before being refluxed at 65°C for 6h. The solution was cooled to rt and then to 0°C at which point it was quenched with 50mL of methanol dropwise over 30 min. A subsequent 150mL of methanol was added and the solution was stirred for 15min before being concentrated under reduced pressure and azeotroped 3 x 200mL methanol. The residue was suspended in 700mL of methanol, treated with 700mL of 10% Rochelle's salt, and refluxed at 80°C for 18h. The solution was cooled to rt and concentrated under reduced pressure. The crude product was extracted from the aqueous mixture with 3 x 700 mL ethyl acetate, washed with 700 mL brine, dried with MgSO₄, and concentrated under reduced pressure to afford 20.2 g of the desired crude material as a clear oil, which was carried on to the next step without further purification. ¹H NMR (300 MHz, CDCl₃) δ 7.79 (m, 2H), 7.21 (m, 4H), 6.86 (m, 2H), 4.44 (s, 2H), 3.91 (m, 1H), 3.79 (s, 3H), 3.32 (m, 2H), 3.06 (m, 1H), 2.78 (m, 6H), 2.48 (dd, *J* = 11.8, 8.0 Hz, 1H), 1.89 (d, *J* = 11.8 Hz, 1H), 0.99 (m, 6H), 0.89 (d, *J* = 4.9 Hz, 9H), 0.09 (dd, *J* = 12.7, 6.8 Hz, 6H). MS (ESI) calcd for C₂₉H₄₇FN₂O₅SSi [M + H]⁺: 583. Found: 583

Synthesis of intermediate M

- 51 -



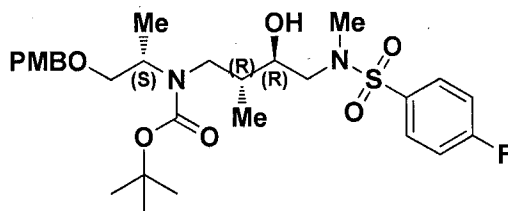
Synthesis of tert-butyl ((2R,3R)-3-((tert-butyldimethylsilyl)oxy)-4-(4-fluoro-N-

5 methylphenylsulfonamido)-2-methylbutyl)((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)carbamate

To a solution of Linear amine K (1.524 g, 2.61 mmol) in DCM (13 ml) was added di-tert-butyl dicarbonate (0.571g, 2.61mmol), followed by triethylamine (0.729 ml, 5.23 mmol). The reaction was stirred at room temperature until completion. The mixture was worked up with water, the layers were separated and the aqueous layer was extracted with DCM. The combined organic layers were dried over Na₂SO₄, filtered and the solvent was removed under pressure. The crude residue was purified by silica gel chromatography using ethyl acetate/hexanes to give 1.445 g of pure product (81% yield). ¹H NMR (300 MHz, CDCl₃) δ 7.80 – 7.63 (m, 2H), 7.25 – 7.01 (m, 4H), 6.89 – 6.69 (d, 2H), 4.38 (s, 2H), 3.86 – 3.77 (m, 1H), 3.75 (s, 3H), 3.70 – 3.46 (m, 2H), 3.43 – 3.24 (m, 1H), 3.23 – 3.02(m, 2H), 2.99 – 2.77 (d, 2H), 2.73(s, 3H), 1.97 (m, 1H), 1.36 (s, 9H), 1.19 (d, 3H), 0.83 (d, 3H), 0.73 (s, 9H), 0.00 (m, 6H). MS (ESI) calculated for C₃₄H₅₅FN₂O₇SSi [M + H]⁺: 683. Found: 683.

20 Intermediate M

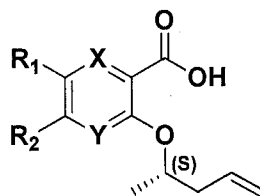
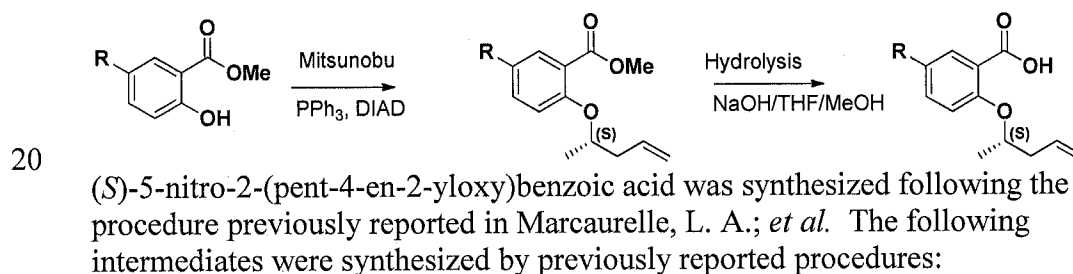
- 52 -

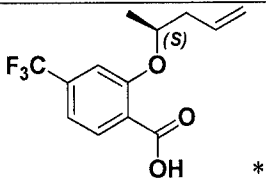
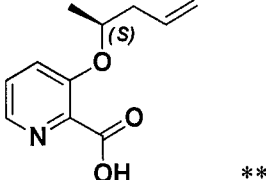
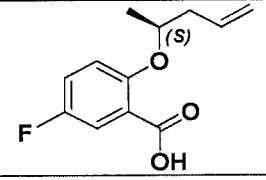
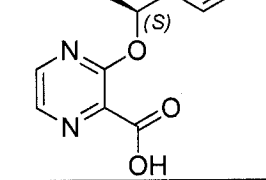
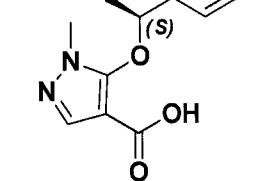
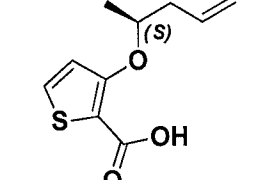
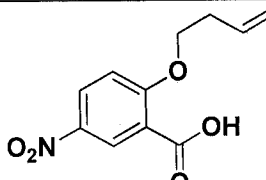
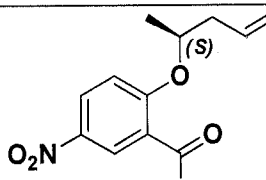


Synthesis of tert-butyl ((2R,3R)-4-(4-fluoro-N-methylphenylsulfonamido)-3-hydroxy-2-methylbutyl)((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)carbamate

To a solution of Linear amine Intermediate L (0.600 g, 0.879 mmol) in THF (6.76 ml) under N₂ was added TBAF (0.636 ml, 2.196 mmol). The reaction was stirred at room temperature overnight. The reaction was then quenched with a saturated ammonium chloride solution and the product was extracted with ethyl acetate. The aqueous layer was washed with ethyl acetate. The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by silica gel chromatography using ethyl acetate/hexanes to afford 0.477g of pure product (95 % yield). ¹H NMR (300 MHz, CDCl₃) δ 7.80 – 7.58 (m, 2H), 7.20 – 6.94 (m, 4H), 6.86 – 6.66 (d, 2H), 4.35 (s, 2H), 3.95 – 3.77 (m, 1H), 3.72 (s, 3H), 3.66 – 3.58 (m, 1H), 3.58 – 3.45 (m, 2H), 3.45 – 3.29 (m, 1H), 3.29 – 3.15 (m, 1H), 3.15 – 2.83 (m, 3H), 2.75 (s, 3H), 1.90 – 1.69 (m, 1H), 1.30 (s, 9H), 1.20 – 1.00 (d, 3H), 0.91 – 0.74 (d, 3H). MS (ESI) calculated for C₂₈H₄₁FN₂O₇S [M + H]⁺: 569. Found: 569.

Synthesis of aryl carboxylic acid intermediate N:

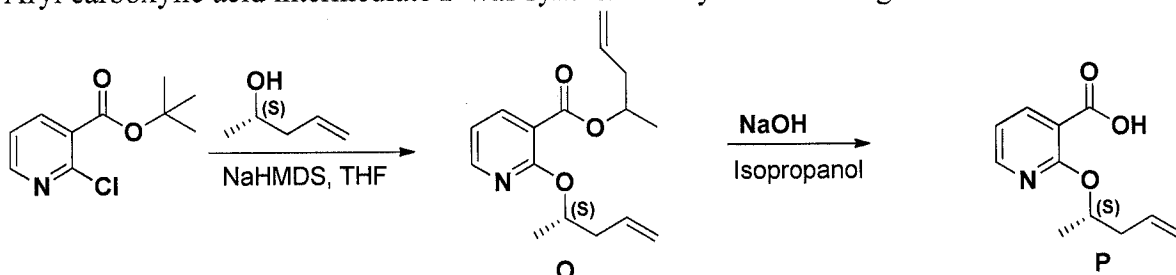


No.	Structure	Name	MS
N1		(S)-2-(pent-4-en-2-yloxy)-4-(trifluoromethyl)benzoic acid	[M-H] ⁻ calcd 273; found, 273
N2		(S)-3-(pent-4-en-2-yloxy)picolinic acid	[M+H] ⁺ calcd 208; found, 208
N3		(S)-5-fluoro-2-(pent-4-en-2-yloxy)benzoic acid	[M+H] ⁺ calcd 225; found, 225
N4		(S)-3-(pent-4-en-2-yloxy)pyrazine-2-carboxylic acid	[M+H] ⁺ calcd 209; found, 209
N5		(S)-1-methyl-5-(pent-4-en-2-yloxy)-1H-pyrazole-4-carboxylic acid	[M+H] ⁺ calcd 211; found, 211
N6		(S)-3-(pent-4-en-2-yloxy)thiophene-2-carboxylic acid	[M+H] ⁺ calcd 212; found, 212
N7		2-(but-3-en-1-yloxy)-5-nitrobenzoic acid	[M+H] ⁺ calcd 238; found, 238
N8		(R)-5-nitro-2-(pent-4-en-2-yloxy)benzoic acid	[M+H] ⁺ calcd 252; found, 252

*methyl 2-hydroxy-5-(trifluoromethyl)benzoate can be prepared as is reported in Gormemis, A.E.; Ha, T.S.; Im, I.; Jung, K.-Y.; Lee, J.Y.; Park, C.-S.; Kim, Y.-C. *ChemBioChem* **2005**, 6, 1745-1748.

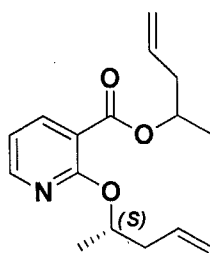
** methyl 3-hydroxypicolinate can be prepared as is reported in Hirashima, S.; Suzuki, T.; Ishida, T.; Noji, S.; Yata, S.; Ando, I.; Komatsu, M.; Ikeda, S.; Hashimoto, H. *J. Med. Chem.* **2006**, *49*, 4721-4736.

- 5 Aryl carboxylic acid intermediate **P** was synthesized by the following method:



- 10 *Tert*-butyl 2-chloronicotinate was synthesized following the procedure previously reported in Kloc, K.; Maliszewka, I.; Mlochowski, J. *Synth. Commun.* **2003**, *33*, 3805-3815.

Intermediate O:



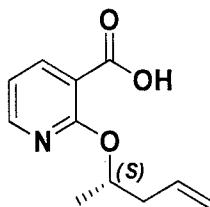
15

Pent-4-en-2-yl 2-((S)-pent-4-en-2-yloxy)nicotinate (O)

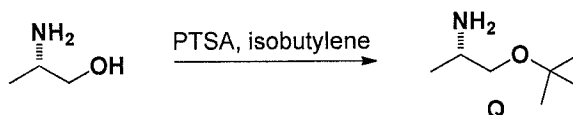
- A solution of (S)-pent-4-en-2-ol (3.85mL, 37.4 mmol 4.0 equiv) in THF (24mL, 0.05 M) was cooled to -8C and treated with 1 molar sodium hexamethyldisilazane in THF (37.4 mL, 37.4 mmol, 4.0 equiv). The reaction was stirred at the reduced temperature for 5 minutes before the ice bath was removed. Stirring was continued for an additional 25 minutes before being treated with a solution of *tert*-butyl 2-chloronicotinate (2.0g, 9.36 mmol, 1 equiv.) in THF (24 mL, 0.05 M). The reaction was stirred for 1 hour at room temperature before being quenched with 50 mL of saturated ammonium chloride. The crude product was extracted with 3 x 60 mL DCM, dried with Na₂SO₄ and concentrated under reduced pressure. This material was chromatographed on silica, eluting with 10–20% ethyl acetate in hexanes to afford 1.7 g (66% yield) of the desired product as a clear oil. ¹H NMR (300 MHz, CDCl₃) δ 8.22 (dd, *J* = 1.3, 4.9, 1H), 8.05 (dd, *J* = 1.4, 7.5, 1H), 6.85 (dd, *J* = 5.2, 7.1, 1H), 5.86 (m, 2H), 5.35 (m, 1H), 5.12 (m, 5H), 2.62 – 2.27 (m, 4H), 1.32 (t, *J* = 5.9, 6H). MS (ESI) calcd for C₁₆H₂₁NO₃ [*M* + *H*]⁺: 276. Found: 276.

Intermediate P:

- 55 -

**(S)-2-(pent-4-en-2-yloxy)nicotinic acid (P)**

To a solution of pent-4-en-2-yl 2-((S)-pent-4-en-2-yloxy)nicotinate (1.7g, 6.17mmol, 1.0 equiv) in isopropanol (20.5 mL, 0.3 M) was added 2 M sodium hydroxide (4 mL, 8.00 mmol, 1.3 equiv). The reaction was stirred for 18 h before being quenched with glacial acetic acid (3.5 mL, 61.7 mmol, 10 equiv) and concentrated under reduced pressure. The crude material was resuspended with 75 mL DCM and partitioned between 30 mL of H₂O. The aqueous layer was washed 2 x 50 mL DCM. The combined organic layers were dried with Na₂SO₄, concentrated under reduced pressure, resuspended in toluene and concentrated under reduced pressure to afford 1.3g of the desired crude material, which was carried on to the next step without further purification. ¹H NMR (300 MHz, CDCl₃) δ 8.44 (dd, *J* = 1.7, 7.6, 1H), 8.33 (dd, *J* = 2.0, 4.8, 1H), 7.08 (dd, *J* = 4.9, 7.5, 1H), 5.81 (m, 1H), 5.61 (dd, *J* = 6.1, 12.3, 1H), 5.26 – 5.08 (m, 2H), 2.53 (m, 2H), 1.45 (d, *J* = 6.3, 3H). MS (ESI) calcd for C₁₁H₁₃NO₃ [M + H]⁺: 208. Found: 208.

Synthesis of *t*-Bu ether Q for preparation of intermediate C4:**tert-butyl((2R,3R)-4-(((S)-1-(tert-butoxy)propan-2-yl)amino)-2-((tert-butyldimethylsilyl)oxy)-3-methylbutyl)(methyl)carbamate (Q)**

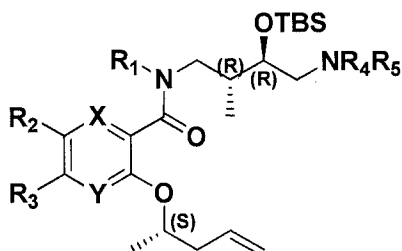
To 4-methylbenzenesulfonic acid (4.59 g, 26.6 mmol) in dry DCM (133 ml) was added (S)-2-aminopropan-1-ol (1.038 ml, 13.31 mmol) at room temperature. Then a balloon of isobutylene gas was added and the resulting solution was purged for 10min, and finally stirred under static isobutylene gas at room temperature for 96h. The solution was purged with nitrogen for 15min and degassed carefully. Around 3/4 volume of solvent was evaporated, then ether (6 X initial volume) was added and crystallization was completed by cooling the mixture to 0°C. The crude was filtered and washed with ether affording the desired product under PTSA salt as white solid (3.61 g, 89%). ¹H NMR (300 MHz, CDCl₃) δ 7.76 (d, *J* = 7.8, 2H), 7.60 (s, 2H), 7.17 (d, *J* = 7.8, 2H), 3.61- 3.19 (m, 4H), 2.36 (s, 4H), 1.32 (d, 3H), 1.10 (s, 7H). MS (ESI) calcd for C₇H₁₇NO [M + H]⁺: 132. Found: 132.

Amide formation:

Intermediates **R1-R8** were synthesized following the procedure previously reported in Marcaurelle, L. A.; Comer, E.; Dandapani, S.; Duvall, J. R.; Gerard, B.; Kesavan,

S.; Lee, M. D, IV; Liu, H.; Lowe, J. T.; Marie, J.-C.; Mulrooney, C. A.; Pandya, B. A.; Rowley, A.; Ryba, T. D.; Suh, B.-C.; Wei, J.; Young, D. W.; Akella, L. B.; Ross, N. B.; Zhang, Y.-L.; Fass, D. M.; Reis, S. A.; Zhao, W.-N.; Haggarty, S. J.; Palmer, M.; Foley, M. A. *J. Am. Chem. Soc.* **2010**, *132*, 16962-16976.

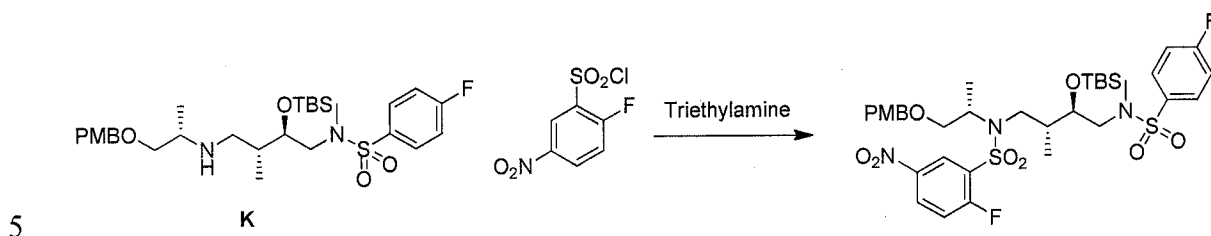
5

Intermediate R:

No.	Structure	Name	MS
R1		tert-butyl ((2R,3R)-2-(((tert-butyldimethylsilyl)oxy)-3-methyl-4-(N-methyl-5-nitro-2-((S)-pent-4-en-2-yloxy)benzamido)butyl)(methyl)carbamate	[M+H] ⁺ calcd 594; found, 594
R2		tert-butyl ((2R,3R)-2-(((tert-butyldimethylsilyl)oxy)-4-(N-isopropyl-5-nitro-2-((S)-pent-4-en-2-yloxy)benzamido)-3-methylbutyl)(methyl)carbamate	[M+H] ⁺ calcd 622; found, 622
R3		tert-butyl ((2R,3R)-2-(((tert-butyldimethylsilyl)oxy)-4-(N-(2-((4-methoxybenzyl)oxy)ethyl)-5-nitro-2-((S)-pent-4-en-2-yloxy)benzamido)-3-methylbutyl)(methyl)carbamate	[M+H] ⁺ calcd 744; found, 744
R4		tert-butyl ((2R,3R)-4-(N-((S)-1-(tert-butoxy)propan-2-yl)-5-nitro-2-((S)-pent-4-en-2-yloxy)benzamido)-2-(((tert-butyldimethylsilyl)oxy)-3-methylbutyl)(methyl)carbamate	[M+H] ⁺ calcd 694; found, 694
R5		tert-butyl ((2R,3S)-2-(((tert-butyldimethylsilyl)oxy)-4-(N-((R)-1-((4-methoxybenzyl)oxy)propan-2-yl)-5-nitro-2-((S)-pent-4-en-2-yloxy)benzamido)-3-methyl-4-oxobutyl)(methyl)carbamate	[M+H] ⁺ calcd 758; found, 758

No.	Structure	Name	MS
R6		N-((2R,3R)-3-((tert-butyldimethylsilyl)oxy)-4-(4-fluoro-N-methylphenylsulfonamido)-2-methylbutyl)-N-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-3-((S)-pent-4-en-2-yloxy)thiophene-2-carboxamide	[M+H] ⁺ calcd 777; found, 777
R7		N-((R)-3-((tert-butyldimethylsilyl)oxy)-4-(4-fluoro-N-methylphenylsulfonamido)butyl)-N-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-5-nitro-2-((S)-pent-4-en-2-yloxy)benzamide	[M+H] ⁺ calcd 802; found, 802
R8		tert-butyl ((2R,3R)-4-(2-(but-3-en-1-yloxy)-N-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-5-nitrobenzamido)-2-((tert-butyldimethylsilyl)oxy)-3-methylbutyl)(methyl)carbamate	[M+H] ⁺ calcd 744; found, 744

Synthesis of Sulphonamide Intermediate S:



Synthesis of N-((2R,3R)-3-((tert-butyldimethylsilyl)oxy)-4-(4-fluoro-N-methylphenylsulfonamido)-2-methylbutyl)-2-fluoro-N-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-5-nitrobenzenesulfonamide

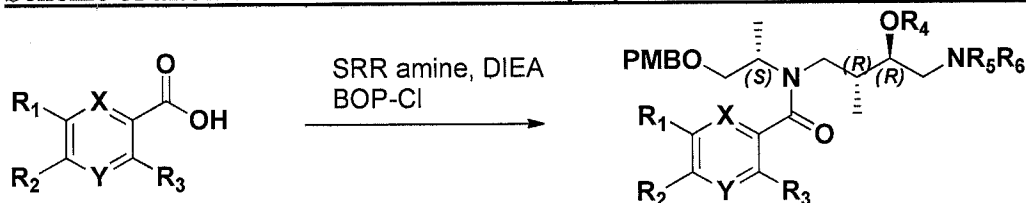
10 To a solution of Linear amine K (0.94 g, 1.613 mmol) in DCM (16.13 ml) was added triethylamine (0.674 ml, 4.84 mmol) followed by 2-fluoro-5-nitrobenzene-1-sulfonyl chloride (0.281 ml, 1.935 mmol). The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was quenched with saturated ammonium chloride and extracted with DCM. The organic components were dried over

15 MgSO₄, filtered and concentrated under reduced pressure. This material was chromatographed on silica, eluting with ethyl acetate in hexanes to afford 1.2 g

- 58 -

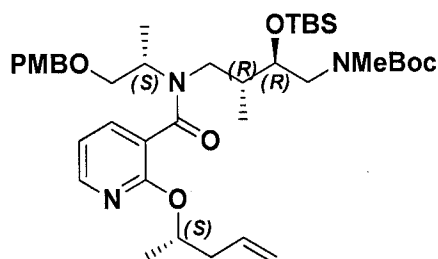
(95% yield) of the desired product as an oil. ^1H NMR (300 MHz, CDCl_3) δ 8.64-8.57 (m, 1H), 7.99 – 7.90 (m, 1H), 7.75 – 7.60 (m, 2H), 7.21-7.09 (m, 2H), 6.93-6.85 (m, 2H), 6.77-6.64 (m, 3H), 4.18 – 3.88 (m, 3H), 3.75 (s, 3H), 3.67-3.45 (m, 2H), 3.35-3.14 (m, 2H), 3.13-3.00 (m, 1H), 2.70 (s, 3H), 2.09 (s, 3H), 1.19 (d, J = 7.0 Hz, 3H), 1.05 (d, J = 6.9 Hz, 3H), 0.85 (s, 9H), 0.01 (d, J = 3.1 Hz, 6H). MS (ESI) calcd for $\text{C}_{35}\text{H}_{49}\text{F}_2\text{N}_3\text{O}_9\text{S}_2\text{Si}$ $[\text{M} + \text{H}]^+$: 786. Found: 786.

Scheme of alternate amide formation for preparation of intermediates R9-R20:



10

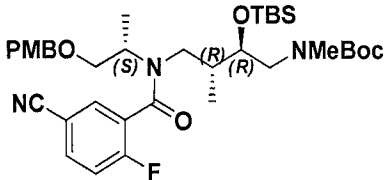
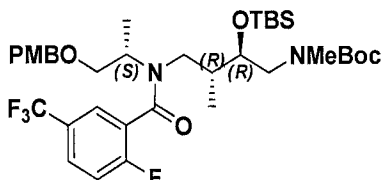
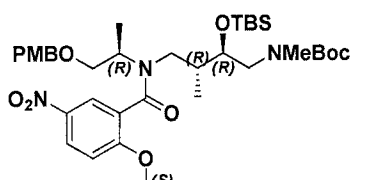
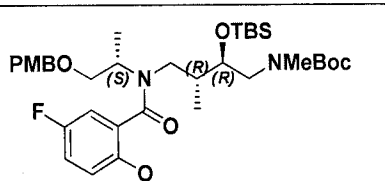
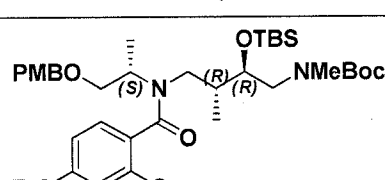
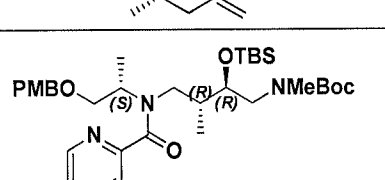
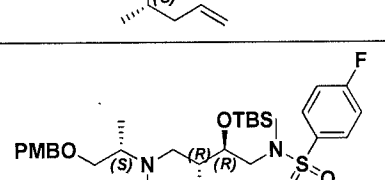
Intermediate R9:



tert-butyl((2R,3R)-2-((tert-butyldimethylsilyl)oxy)-4-(N-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2-((S)-pent-4-en-2-yloxy)nicotinamido)-3-methylbutyl)(methyl)carbamate (R9)

To a solution of (S)-2-(pent-4-en-2-yloxy)nicotinic acid (3.65 g, 17.61 mmol) in 147 mL of DCM at 0 °C was added DIEA (8.97 mL, 51.4 mmol), secondary amine (7.70 g, 14.68 mmol) followed by BOP-Cl (4.48 g, 17.61 mmol). After stirring at reduced temperature for 10 minutes the ice water bath was removed and stirring was continued at room temperature for 90 minutes. Saturated ammonium chloride solution (~ 40 mL) was then added and the reaction was partitioned. The aqueous layer was washed with 2 x 40 mL DCM and the combined organics were dried over sodium sulfate and concentrated. The material was then brought on crude to the next reaction. ^1H NMR (300 MHz, CDCl_3) δ 8.21 – 7.97 (br, 1H), 7.55 – 7.31 (m, 1H), 7.16 – 7.03 (m, 2H), 6.93 – 6.65 (m, 3H), 5.92 – 5.65 (m, 1H), 5.42 – 5.16 (m, 1H), 5.12 – 4.96 (m, 2H), 4.56 – 4.21 (m, 2H), 4.20 – 3.82 (m, 1H), 3.78 (s, 3H), 3.74 – 3.58 (m, 1H), 3.54 – 3.22 (m, 2H), 3.19 – 2.99 (m, 2H), 2.96 – 2.64 (m, 3H), 2.60 – 2.18 (m, 3H), 1.54 – 1.31 (m, 9H), 1.35 – 0.95 (m, 9H), 0.89 (s, 6H), 0.64 (s, 3H), 0.05 (s, 2H), 0.03 (s, 2H), -0.09 (s, 1H), -0.19 (s, 1H). MS (ESI) calcd for $\text{C}_{39}\text{H}_{63}\text{N}_3\text{O}_7\text{Si}$ $[\text{M} + \text{H}]^+$: 715. Found: 715.

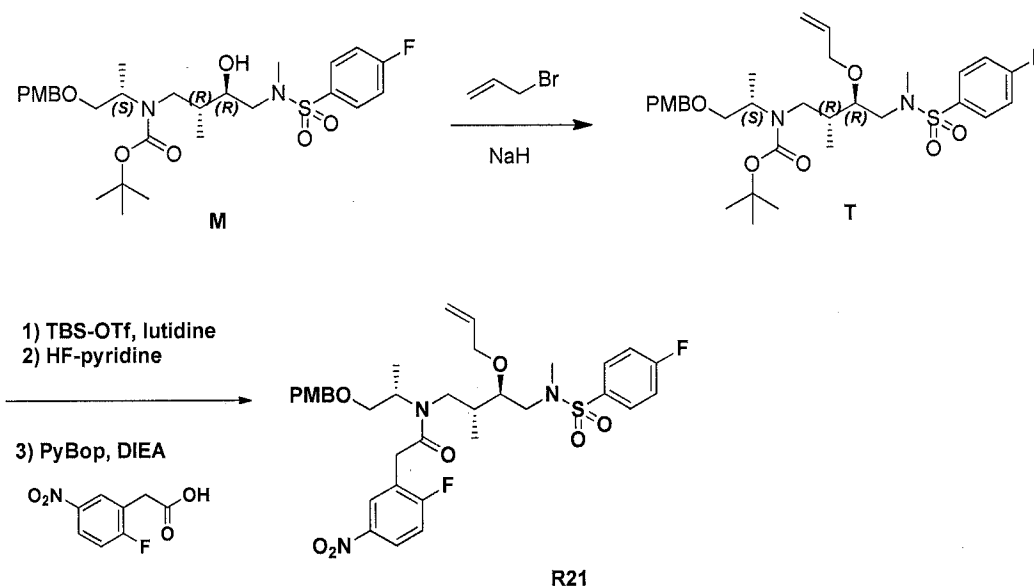
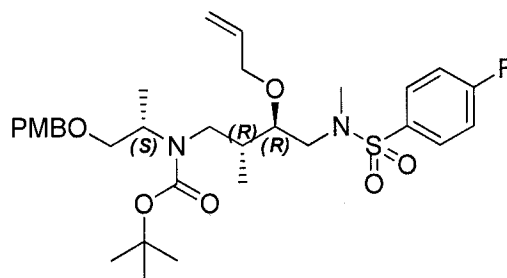
The following intermediates were prepared using this method:

No.	Structure	Name	MS
R10		tert-butyl ((2R,3R)-2-((tert-butyldimethylsilyl)oxy)-4-(5-cyano-2-fluoro-N-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)benzamido)-3-methylbutyl)(methyl)carbamate	[M+H] ⁺ calcd 672; found, 672
R11		tert-butyl ((2R,3R)-2-((tert-butyldimethylsilyl)oxy)-4-(2-fluoro-N-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-5-(trifluoromethyl)benzamido)-3-methylbutyl)(methyl)carbamate	[M+H] ⁺ calcd 715; found, 715
R12		tert-butyl ((2R,3R)-2-((tert-butyldimethylsilyl)oxy)-4-(N-((R)-1-((4-methoxybenzyl)oxy)propan-2-yl)-5-nitro-2-((S)-pent-4-en-2-yloxy)benzamido)-3-methylbutyl)(methyl)carbamate	[M+H] ⁺ calcd 758; found, 758
R13		tert-butyl ((2R,3R)-2-((tert-butyldimethylsilyl)oxy)-4-(4-fluoro-N-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2-((S)-pent-4-en-2-yloxy)benzamido)-3-methylbutyl)(methyl)carbamate	[M+H] ⁺ calcd 731; found, 731
R14		tert-butyl ((2R,3R)-2-((tert-butyldimethylsilyl)oxy)-4-(N-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2-((S)-pent-4-en-2-yloxy)-4-(trifluoromethyl)benzamido)-3-methylbutyl)(methyl)carbamate	[M+H] ⁺ calcd 781; found, 781
R15		tert-butyl ((2R,3R)-2-((tert-butyldimethylsilyl)oxy)-4-(N-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-3-((S)-pent-4-en-2-yloxy)picolinamido)-3-methylbutyl)(methyl)carbamate	[M+H] ⁺ calcd 714; found, 714
R16		N-((2R,3R)-3-((tert-butyldimethylsilyl)oxy)-4-(4-fluoro-N-methylphenylsulfonamido)-2-methylbutyl)-N-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-3-((S)-pent-4-en-2-yloxy)pyrazine-2-carboxamide	[M+H] ⁺ calcd 773; found, 773

No.	Structure	Name	MS
R17		N-((2R,3R)-3-((tert-butyldimethylsilyloxy)-4-(4-fluoro-N-methylphenylsulfonamido)-2-methylbutyl)-N-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-1-methyl-5-((S)-pent-4-en-2-yloxy)-1H-pyrazole-4-carboxamide	[M+H] ⁺ calcd 775; found, 775
R18		tert-butyl ((2R,3R)-2-hydroxy-4-(N-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-5-nitro-2-((S)-pent-4-en-2-yloxy)benzamido)-3-methylbutyl)carbamate	[M+H] ⁺ calcd 630; found, 630
R19		N-((2R,3R)-3-(tert-butyldimethylsilyloxy)-4-(4-fluoro-N-methylphenylsulfonamido)-2-methylbutyl)-N-((S)-1-((4-methoxybenzyloxy)propan-2-yl)-5-nitro-2-((R)-pent-4-en-2-yloxy)benzamide	[M+H] ⁺ calcd 816; found, 816
R20		N-((2R,3R)-3-((tert-butyldimethylsilyl)oxy)-4-(4-fluoro-N-methylphenylsulfonamido)-2-methylbutyl)-2-fluoro-N-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-5-nitrobenzamide	[M+H] ⁺ calcd 750; found, 750

Scheme of alternate amide formation for preparation of intermediate R21:

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**Intermediate T:**

5 **Synthesis of tert-butyl ((2R,3R)-3-(allyloxy)-4-(4-fluoro-N-methylphenylsulfonamido)-2-methylbutyl)((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)carbamate**

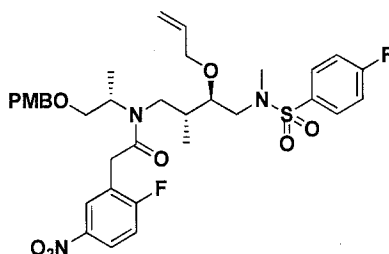
To a solution of **M** (0.719 g, 1.264 mmol) in DMF (8.43 ml) at 0 °C was added 3-bromoprop-1-ene (0.321 ml, 3.79 mmol) followed by sodium hydride (0.101 g, 2.53 mmol). After 7 h further sodium hydride (0.050 g, 1.26 mmol) was added. After 24 h the reaction was quenched with saturated ammonium chloride solution (8 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were dried with magnesium sulfate, concentrated and subjected to chromatography on silica, using Hexane/Ethyl acetate to give the desired product (0.685 g, 89%) as colorless resin.

15 ¹H NMR (300 MHz, CDCl₃) δ 7.84-7.79 (m, 2H), 7.40-7.04 (m, 4H), 6.88 (d, J = 8.5 Hz, 2H), 5.91-5.78 (m, 1H), 5.62-4.84 (m, 2H), 4.45 (s, 2H), 4.00 (d, J = 4.5 Hz, 2H), 3.80 (s, 3H), 3.71-3.56 (m, 2H), 3.54-3.38 (m, 2H), 3.28-3.03 (s, 3H), 2.83 (s, 3H), 2.29-1.98 (s, 2H), 1.44 (s, 9H), 1.24 (d, J = 6.7 Hz, 3H), 0.92 (d, J = 6.8 Hz, 3H). MS (ESI) calcd for C₃₁H₄₅FN₂O₇S [M + H]⁺: 609. Found: 609.

20

Intermediate R21

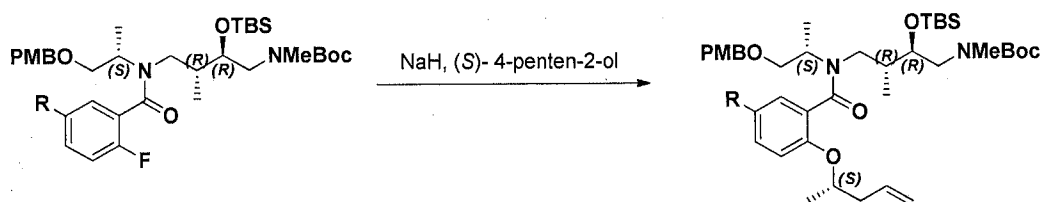
- 62 -



Synthesis of N-((2R,3R)-3-(allyloxy)-4-(4-fluoro-N-methylphenylsulfonamido)-2-methylbutyl)-2-(2-fluoro-5-nitrophenyl)-N-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)acetamide

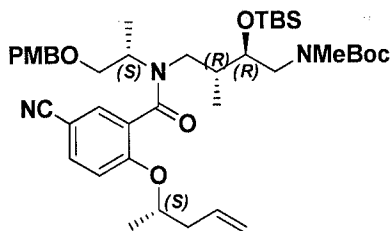
To a solution of **T** (0.685 g, 1.125 mmol) in DCM (22.50 ml) at 0°C was added 2,6-dimethylpyridine (0.524 ml, 4.50 mmol), followed by TBS-triflate (0.647 ml, 2.81 mmol). The reaction was stirred for 2h. 2,6-dimethylpyridine (0.524 ml, 4.50 mmol) was then added, and the reaction was quenched with saturated ammonium chloride. The layers were separated, and the aqueous layer was extracted with DCM (3 X 30 mL). The combined organics were dried, filtered, and concentrated under reduced pressure and the crude residue was used in the next step. This crude material was dissolved in THF (20.0 ml) in a plastic bottle and cooled to 0 °C before adding a 70% HF-Pyridine solution (0.147 ml, 1.181 mmol). The reaction was stirred for 1h and was then quenched with saturated ammonium chloride and extracted with EtOAc. The combined organics were dried, filtered and concentrated under reduced pressure and the crude residue was used directly in the subsequent reaction. To a solution of this crude material (0.606 g, 1.191 mmol), N-ethyl-N-isopropylpropan-2-amine (0.623 ml, 3.57 mmol), and 2-(2-fluoro-5-nitrophenyl)acetic acid (0.273 g, 1.370 mmol) in DCM (11.91 ml) at 0 °C was added PyBOP (0.744 g, 1.430 mmol) as a solid in one portion. The reaction was stirred for 2h. The reaction was then concentrated under reduced pressure and the crude residue was chromatographed on silica, eluting with 10–20% ethyl acetate in hexanes to afford 0.630 g (81% yield) of the desired product. ¹H NMR (300 MHz, CDCl₃) δ 8.29 – 8.01 (m, 2H), 7.87–7.66 (m, 2H), 7.32–7.06 (m, 5H), 6.89 (m, 2H), 5.96–5.73 (m, 1H), 5.36 – 5.07 (m, 2H), 4.50–5.41 (m, 2H), 4.32 – 4.19 (m, 1H), 4.18 – 3.85 (m, 4H), 3.81–3.79 (m, 3H), 3.66 – 3.27 (m, 4H), 3.25 – 3.11 (m, 2H), 3.07–2.92 (m, 1H), 2.80–2.79 (m, 3H), 2.33–2.16 (m, 1H), 1.41–1.18 (m, 3H), 1.17–0.85 (m, 3H). MS calculated for C₃₄H₄₁F₂N₃O₈S [M+H]⁺: 690. Found: 690.

SNAr reaction to prepare intermediate R22 and R23:



Intermediate R22 :

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5 **tert-butyl((2R,3R)-2-((tert-butyldimethylsilyl)oxy)-4-(5-cyano-N-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2-((S)-pent-4-en-2-yloxy)benzamido)-3-methylbutyl)(methyl)carbamate (R22)**

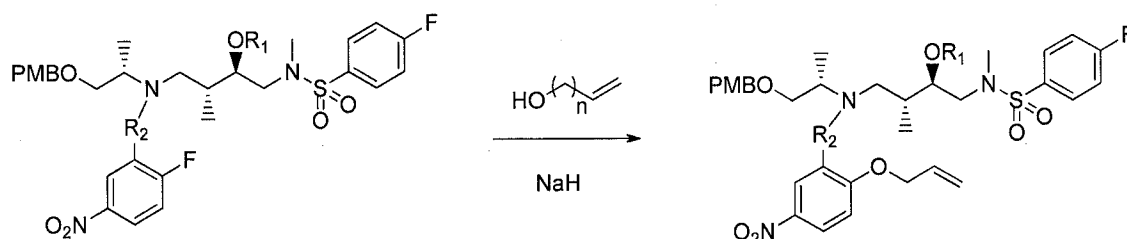
To a solution of (S) + 4-penten-2-ol (15.93 μ l, 0.16 mmol) in THF (298 μ l) was added sodium hydride (6.19 mg, 0.16 mmol) and the mixture was stirred for 20 min. To this solution was added tert-butyl((2R,3R)-2-((tert-butyldimethylsilyl)oxy)-4-(5-cyano-2-fluoro-N-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)benzamido)-3-methylbutyl)(methyl)carbamate in 0.3 mL THF dropwise at 0°C. The reaction was allowed to stir for 2 hours at room temperature. Rxn was then quenched with water, the organic component was extracted with ethyl acetate dried over sodium sulfate and evaporated under reduced pressure. The reaction was purified by column chromatography using Ethylacetate/hexane to afford the desired product (267 mg, 79 %). ¹H NMR (300 MHz, CDCl₃) δ 7.59–7.30 (m, 2H), 7.27–7.05 (m, 2H), 6.99–6.72 (m, 3H), 5.87–5.54 (m, 1H), 5.19–4.90 (m, 2H), 4.60–4.37 (m, 1H), 4.36–4.19 (m, 1H), 4.18–3.88 (m, 4H), 3.81–3.49 (m, 3H), 3.51–2.93 (m, 3H), 2.93–2.67 (m, 2H), 2.66–2.17 (m, 2H), 2.13 (s, 1H), 1.66–1.36 (m, 7H), 1.29–0.93 (m, 14H), 0.92–0.74 (m, 6H), 0.71–0.48 (m, 3H), 0.11– -0.04 (m, 3H), -0.09– -0.4 (m, 3H). MS (ESI) calcd for C₄₁H₆₃N₃O₇Si [M + H]⁺: 738. Found: 738.

The following intermediate was also prepared using this method:

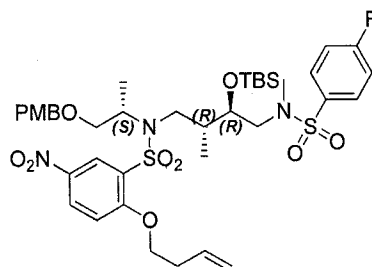
No.	Structure	Name	MS
R23		tert-butyl ((2R,3R)-2-((tert-butyldimethylsilyl)oxy)-4-(N-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2-((S)-pent-4-en-2-yloxy)-5-(trifluoromethyl)benzamido)-3-methylbutyl)(methyl)carbamate	[M+H] ⁺ calcd 781; found, 781

Alternative S_NAr reaction with allyl alcohol To prepare intermediates R24-R27

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Intermediate R24:



5

Synthesis of 2-(but-3-en-1-yloxy)-N-((2R,3R)-3-((tert-butyldimethylsilyl)oxy)-4-(4-fluoro-N-methylphenylsulfonamido)-2-methylbutyl)-N-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-5-nitrobenzenesulfonamide

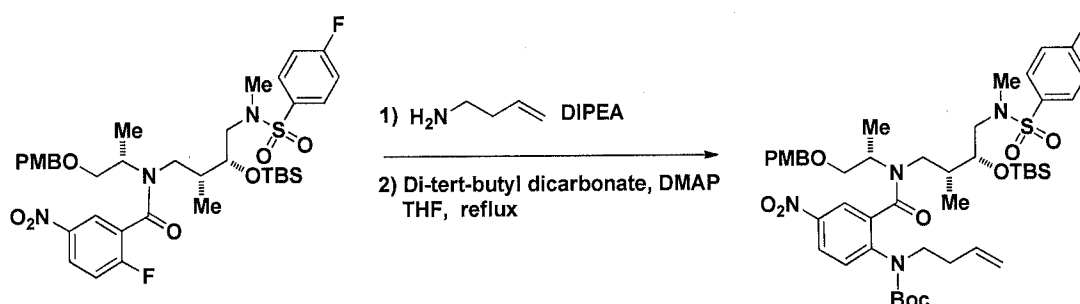
To a solution of but-3-en-1-ol (0.246 ml, 2.88 mmol) in THF (14.38 ml) was added sodium hydride (0.115 g, 2.88 mmol) at 0°C and the mixture was stirred for 20 min. To this was added S (1.13 g, 1.438 mmol) in THF (3 ml) dropwise over 5 min. The reaction was stirred at 0°C for 40 mins. The reaction was quenched with water after 2h, the organic component was extracted with ethyl acetate dried and was purified by column chromatography using Ethylacetate/hexane to afford the desired product (1.19g, 99 %). ¹H NMR (300 MHz, CDCl₃) δ 8.72 (d, *J* = 2.8, 1H), 8.13 (dd, *J* = 9.1, 2.8, 1H), 7.75-7.63 (m, 2H), 7.17 (t, *J* = 8.5, 2H), 6.92 (d, *J* = 8.5, 2H), 6.72 (d, *J* = 8.5, 2H), 6.67 (d, *J* = 9.2, 1H), 5.90-6.71 (m, 1H), 5.19-4.99 (m, 2H), 4.15 (q, *J* = 11.1, 2H), 3.94 – 3.77 (m, 4H), 3.73 (s, 3H), 3.65-3.43 (m, 2H), 3.44-3.30 (m, 1H), 3.28-3.09 (m, 2H), 2.68 (s, 3H), 2.65-2.51 (m, 3H), 2.13-1.98 (m, 1H), 1.96 (s, 3H), 1.03 (d, *J* = 6.9, 3H), 0.83 (s, 9H), 0.00 (s, 6H). MS calculated for C₃₉H₅₆FN₃O₁₀S₂Si : [M+Na]⁺ 860. Found: 860.

20

No.	Structure	Name	MS
R25		N-((2R,3R)-3-(allyloxy)-4-(4-fluoro-N-methylphenylsulfonamido)-2-methylbutyl)-2-(2-(allyloxy)-5-nitrophenyl)-N-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)acetamide	[M+H] ⁺ calcd 728; found, 728.

No.	Structure	Name	MS
R26		N-((2R,3R)-3-(allyloxy)-4-(4-fluoro-N-methylphenylsulfonamido)-2-methylbutyl)-2-(2-(but-3-en-1-yloxy)-5-nitrophenyl)-N-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)acetamide	[M+H] ⁺ calcd 742; found, 742.
R27		2-(allyloxy)-N-((2R,3R)-3-((tert-butyldimethylsilyl)oxy)-4-(4-fluoro-N-methylphenylsulfonamido)-2-methylbutyl)-N-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-5-nitrobenzamide	[M+H] ⁺ calcd 788; found, 788

Alternative SNAr reaction and Boc protection to prepare intermediate R28:



5

Synthesis of tert-butyl but-3-en-1-yl(2-(((2R,3R)-3-((tert-butyldimethylsilyl)oxy)-4-(4-fluoro-N-methylphenylsulfonamido)-2-methylbutyl)((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)carbamoyl)-4-nitrophenyl)carbamate

To a solution of N-((2R,3R)-3-((tert-butyldimethylsilyl)oxy)-4-(4-fluoro-N-methylphenylsulfonamido)-2-methylbutyl)-2-(2-(but-3-en-1-yloxy)-5-nitrophenyl)-N-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-5-nitrobenzamide R20 (228 mg, 0.304 mmol) in DMF (7239 μ l) was added DIEA (82 μ l, 0.471 mmol) and but-3-en-1-amine (78 μ l, 0.851 mmol) at room temperature. The rxn was then heated to 35 $^{\circ}$ C. After 2 h further but-3-en-1-amine (78 μ l, 0.851 mmol) and DIEA (82 μ l, 0.471 mmol) were added. After 5h the reaction was evaporated under reduced pressure. The reaction was purified by column chromatography using using Ethylacetate/hexane to afford the desired product. (220 mg, 90%). ¹H NMR (300 MHz, CDCl₃) δ 8.09-7.99 (m, 2H), 7.75-7.65 (m, 2H), 7.37 – 6.99 (m, 4H), 6.84-6.75 (m, 2H), 6.49 (d, *J* = 8.7, 1H), 5.74-5.56 (m, 1H), 5.02 (dd, *J* = 13.6, 2.0, 2H), 4.51-4.28 (m, 2H), 3.72 (s, 3H), 3.51-3.20 (m, 2H), 3.16-3.00 (m, 4H), 2.96 – 2.52 (m, 4H), 2.23 – 1.97 (m, 5H), 1.85 – 1.30 (m, 7H), 1.02 – 0.42 (m, 9H), 0.14 – -0.42(m, 6H). MS (ESI) calcd for

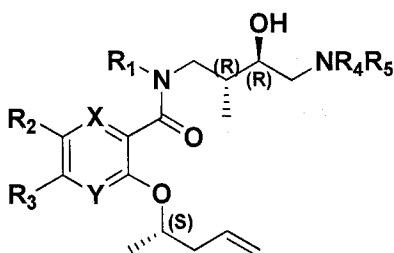
- 66 -

$C_{40}H_{57}FN_4O_8SSi$ $[M + H]^+$: 801. Found: 801. To a solution of this material (20 mg, 0.025 mmol) in THF (250 μ l) was added di-tert-butyl dicarbonate (21.80 mg, 0.100 mmol) and DMAP (0.610 mg, 4.99 μ mol) and the reaction was heated to reflux for 1 hour. The reaction mixture was then concentrated under reduced pressure. This mixture was purified by column chromatography using Ethylacetate/hexane to afford the desired product (16 mg, 71 %). 1H NMR (300 MHz, $CDCl_3$) δ 8.45-8.24 (m, 1H), 8.13-7.97 (m, 1H), 7.77-7.60 (m, 2H), 7.22 - 7.01 (m, 5H), 6.85 - 6.67 (m, 2H), 5.72 - 5.53 (m, 1H), 5.03 - 4.89 (m, 2H), 4.46 - 4.22 (m, 2H), 4.15 - 3.93 (m, 1H), 3.87-3.75 (m, 1H), 3.70 (s, 3H), 3.40-3.23 (m, 2H), 3.22-3.01 (m, 2H), 2.98-2.84 (m, 2H), 2.71 (s, 3H), 2.27-2.03 (m, 3H), 1.71 - 1.53 (m, 2H), 1.50 - 1.18 (m, 12H), 1.03-0.90 (m, 3H), 0.82 (s, 9H), 0.06 - -0.08 (m, 6H). MS (ESI) calcd for $C_{45}H_{65}FN_4O_{10}SSi$ $[M + H]^+$: 901. Found: 901.

Deprotection of TBS ether:

Intermediates **T1-T19** were synthesized following the procedure previously reported in Marcaurelle, L. A.; Comer, E.; Dandapani, S.; Duvall, J. R.; Gerard, B.; Kesavan, S.; Lee, M. D, IV; Liu, H.; Lowe, J. T.; Marie, J.-C.; Mulrooney, C. A.; Pandya, B. A.; Rowley, A.; Ryba, T. D.; Suh, B.-C.; Wei, J.; Young, D. W.; Akella, L. B.; Ross, N. B.; Zhang, Y.-L.; Fass, D. M.; Reis, S. A.; Zhao, W.-N.; Haggarty, S. J.; Palmer, M.; Foley, M. A. *J. Am. Chem. Soc.* **2010**, *132*, 16962-16976.

Intermediate T:



25

No.	Structure	Name	MS
T1		tert-butyl ((2R,3R)-2-hydroxy-4-(N-isopropyl-5-nitro-2-((S)-pent-4-en-2-yloxy)benzamido)-3-methylbutyl)(methyl)carbamate	$[M+H]^+$ calcd 508; found, 508
T2		tert-butyl ((2R,3R)-2-hydroxy-4-(N-((R)-1-((4-methoxybenzyl)oxy)propan-2-yl)-5-nitro-2-((S)-pent-4-en-2-yloxy)benzamido)-3-methylbutyl)(methyl)carbamate	$[M+H]^+$ calcd 644; found, 644

No.	Structure	Name	MS
T3		tert-butyl ((2R,3R)-2-hydroxy-4-(N-(2-((4-methoxybenzyl)oxy)ethyl)-5-nitro-2-((S)-pent-4-en-2-yloxy)benzamido)-3-methylbutyl)(methyl)carbamate	[M+H] ⁺ calcd 630; found, 630
T4		tert-butyl ((2R,3R)-4-(N-((S)-1-(tert-butoxy)propan-2-yl)-5-nitro-2-((S)-pent-4-en-2-yloxy)benzamido)-2-hydroxy-3-methylbutyl)(methyl)carbamate	[M+H] ⁺ calcd 580; found, 580
T5		tert-butyl ((2R,3R)-2-hydroxy-4-(N-((R)-1-((4-methoxybenzyl)oxy)propan-2-yl)-5-nitro-2-((S)-pent-4-en-2-yloxy)benzamido)-3-methylbutyl)(methyl)carbamate	[M+H] ⁺ calcd 644; found, 644
T6		tert-butyl ((2R,3R)-2-hydroxy-4-(N-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2-((S)-pent-4-en-2-yloxy)nicotinamido)-3-methylbutyl)(methyl)carbamate	[M+H] ⁺ calcd 600; found, 600
T7		tert-butyl ((2R,3R)-4-(4-fluoro-N-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2-((S)-pent-4-en-2-yloxy)benzamido)-2-hydroxy-3-methylbutyl)(methyl)carbamate	[M+H] ⁺ calcd 617; found, 617
T8		tert-butyl ((2R,3R)-2-hydroxy-4-(N-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2-((S)-pent-4-en-2-yloxy)-4-(trifluoromethyl)benzamido)-3-methylbutyl)(methyl)carbamate	[M+H] ⁺ calcd 667; found, 667
T9		tert-butyl ((2R,3R)-2-hydroxy-4-(N-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-3-((S)-pent-4-en-2-yloxy)picolinamido)-3-methylbutyl)(methyl)carbamate	[M+H] ⁺ calcd 600; found, 600

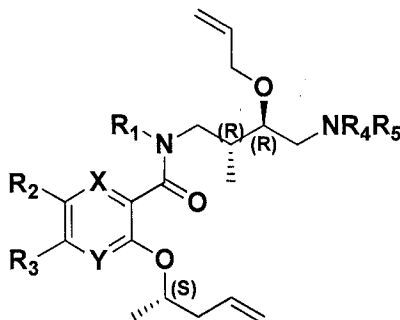
No.	Structure	Name	MS
T10		tert-butyl ((2R,3R)-4-(5-cyano-N-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2-((S)-pent-4-en-2-yloxy)benzamido)-2-hydroxy-3-methylbutyl)(methyl)carbamate	[M+H] ⁺ calcd 624; found, 624
T11		tert-butyl ((2R,3R)-2-hydroxy-4-(N-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2-((S)-pent-4-en-2-yloxy)-4-(trifluoromethyl)benzamido)-3-methylbutyl)(methyl)carbamate	[M+H] ⁺ calcd 667; found, 667
T12		tert-butyl but-3-en-1-yl(2-(((2R,3R)-4-(4-fluoro-N-methylphenylsulfonamido)-3-hydroxy-2-methylbutyl)((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)carbamoyl)-4-nitrophenyl)carbamate	[M+H] ⁺ calcd 787; found, 787
T13		N-((2R,3R)-4-(4-fluoro-N-methylphenylsulfonamido)-3-hydroxy-2-methylbutyl)-N-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-3-((S)-pent-4-en-2-yloxy)pyrazine-2-carboxamide	[M+H] ⁺ calcd 659; found, 659
T14		2-(but-3-en-1-yloxy)-N-((2R,3R)-4-(4-fluoro-N-methylphenylsulfonamido)-3-hydroxy-2-methylbutyl)-N-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-5-nitrobenzenesulfonamide	[M+H] ⁺ calcd 724; found, 724

No.	Structure	Name	MS
T15		N-((2R,3R)-4-(4-fluoro-N-methylphenylsulfonamido)-3-hydroxy-2-methylbutyl)-N-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-1-methyl-5-((S)-pent-4-en-2-yloxy)-1H-pyrazole-4-carboxamide	[M+H]⁺ calcd 661; found, 661
T16		tert-butyl ((2R,3R)-4-(2-(but-3-en-1-yloxy)-N-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-5-nitrobenzamido)-2-hydroxy-3-methylbutyl)(methyl)carbamate	[M+H]⁺ calcd 630; found, 630
T17		2-(allyloxy)-N-((2R,3R)-4-(4-fluoro-N-methylphenylsulfonamido)-3-hydroxy-2-methylbutyl)-N-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-5-nitrobenzamide	[M+H]⁺ calcd 674; found, 674
T18		N-((R)-4-(4-fluoro-N-methylphenylsulfonamido)-3-hydroxybutyl)-N-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-5-nitro-2-((S)-pent-4-en-2-yloxy)benzamide	[M+H]⁺ calcd 688; found, 688

No.	Structure	Name	MS
T19		N-((2R,3R)-4-(4-fluoro-N-methylphenylsulfonamido)-3-hydroxy-2-methylbutyl)-N-((S)-1-(4-methoxybenzyloxy)propan-2-yl)-5-nitro-2-((R)-pent-4-en-2-yloxy)benzamide	[M+H] ⁺ calcd 702; found, 702

Allylation:

- Intermediates **U1-U21** were synthesized following the procedure previously reported in Marcaurelle, L. A.; Comer, E.; Dandapani, S.; Duvall, J. R.; Gerard, B.; Kesavan, S.; Lee, M. D, IV; Liu, H.; Lowe, J. T.; Marie, J.-C.; Mulrooney, C. A.; Pandya, B. A.; Rowley, A.; Ryba, T. D.; Suh, B.-C.; Wei, J.; Young, D. W.; Akella, L. B.; Ross, N. B.; Zhang, Y.-L.; Fass, D. M.; Reis, S. A.; Zhao, W.-N.; Haggarty, S. J.; Palmer, M.; Foley, M. A. *J. Am. Chem. Soc.* **2010**, *132*, 16962-16976.

Intermediate UI:

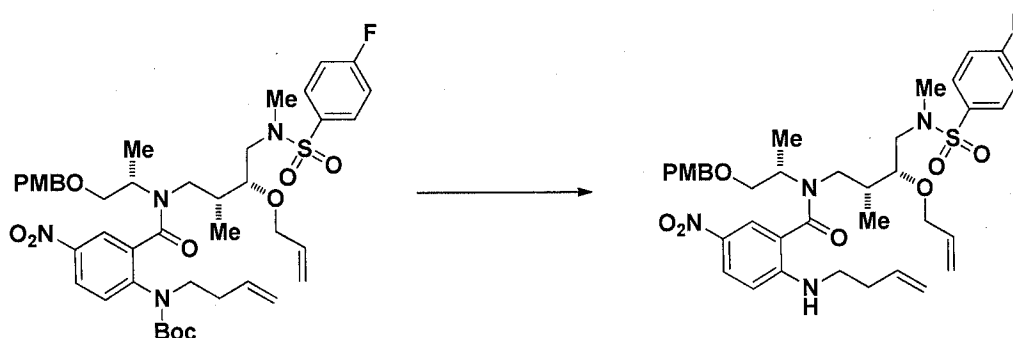
No.	Structure	Name	MS
U1		tert-butyl ((2R,3R)-2-(allyloxy)-3-methyl-4-(N-methyl-5-nitro-2-((S)-pent-4-en-2-yloxy)benzamido)butyl)(methyl)carbamate	[M+H] ⁺ calcd 520; found, 520
U2		tert-butyl ((2R,3R)-2-(allyloxy)-4-(N-isopropyl-5-nitro-2-((S)-pent-4-en-2-yloxy)benzamido)-3-methylbutyl)(methyl)carbamate	[M+H] ⁺ calcd 548; found, 548

No.	Structure	Name	MS
U3		tert-butyl ((2R,3R)-2-(allyloxy)-4-(N-(2-((4-methoxybenzyl)oxy)ethyl)-5-nitro-2-((S)-pent-4-en-2-yloxy)benzamido)-3-methylbutyl)(methyl)carbamate	[M+H] ⁺ calcd 670; found, 670
U4		tert-butyl ((2R,3R)-2-(allyloxy)-4-(N-((S)-1-(tert-butoxy)propan-2-yl)-5-nitro-2-((S)-pent-4-en-2-yloxy)benzamido)-3-methylbutyl)(methyl)carbamate	[M+H] ⁺ calcd 620; found, 620
U5		tert-butyl (2R,3R)-2-(allyloxy)-4-(N-((S)-1-(4-methoxybenzyloxy)propan-2-yl)-2-((S)-pent-4-en-2-yloxy)nicotinamido)-3-methylbutyl(methyl)carbamate	[M+H] ⁺ calcd 640; found, 640
U6		tert-butyl ((2R,3R)-2-(allyloxy)-4-(N-((R)-1-((4-methoxybenzyl)oxy)propan-2-yl)-5-nitro-2-((S)-pent-4-en-2-yloxy)benzamido)-3-methylbutyl)(methyl)carbamate	[M+H] ⁺ calcd 684; found, 684
U7		tert-butyl ((2R,3R)-2-(allyloxy)-4-(5-fluoro-N-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2-((S)-pent-4-en-2-yloxy)benzamido)-3-methylbutyl)(methyl)carbamate	[M+H] ⁺ calcd 657; found, 657
U8		tert-butyl ((2R,3R)-2-(allyloxy)-4-(N-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2-((S)-pent-4-en-2-yloxy)-4-(trifluoromethyl)benzamido)-3-methylbutyl)(methyl)carbamate	[M+H] ⁺ calcd 707; found, 707

No.	Structure	Name	MS
U9		tert-butyl ((2R,3R)-2-(allyloxy)-4-(N-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-3-((S)-pent-4-en-2-yloxy)picolinamido)-3-methylbutyl)(methyl)carbamate	$[M+H]^+$ calcd 640; found, 640
U10		tert-butyl ((2R,3R)-2-(allyloxy)-4-(N-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2-((S)-pent-4-en-2-yloxy)-5-(trifluoromethyl)benzamido)-3-methylbutyl)(methyl)carbamate	$[M+H]^+$ calcd 706; found, 706
U11		tert-butyl ((2R,3R)-2-(allyloxy)-4-(5-cyano-N-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2-((S)-pent-4-en-2-yloxy)benzamido)-3-methylbutyl)(methyl)carbamate	$[M+H]^+$ calcd 664; found, 664
U12		tert-butyl (2-(((2R,3R)-3-(allyloxy)-4-(4-fluoro-N-methylphenylsulfonamido)-2-methylbutyl)((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)carbamoyl)-4-nitrophenyl)(but-3-en-1-yl)carbamate	$[M+H]^+$ calcd 827; found, 827
U13		N-((2R,3R)-3-(allyloxy)-4-(4-fluoro-N-methylphenylsulfonamido)-2-methylbutyl)-N-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-3-((S)-pent-4-en-2-yloxy)pyrazine-2-carboxamide	$[M+H]^+$ calcd 699; found, 699
U14		N-((2R,3R)-3-(allyloxy)-4-(4-fluoro-N-methylphenylsulfonamido)-2-methylbutyl)-2-(but-3-en-1-yloxy)-N-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-5-nitrobenzenesulfonamide	$[M+Na]^+$ calcd 786; found, 786

No.	Structure	Name	MS
U15		N-((2R,3R)-3-(allyloxy)-4-(4-fluoro-N-methylphenylsulfonamido)-2-methylbutyl)-N-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-3-((S)-pent-4-en-2-yloxy)thiophene-2-carboxamide	[M+Na] ⁺ calcd 703; found, 703
U16		N-((2R,3R)-3-(allyloxy)-4-(4-fluoro-N-methylphenylsulfonamido)-2-methylbutyl)-N-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-1-methyl-5-((S)-pent-4-en-2-yloxy)-1H-pyrazole-4-carboxamide	[M+Na] ⁺ calcd 701; found, 701
U17		tert-butyl ((2R,3R)-2-(allyloxy)-4-(2-(but-3-en-1-yloxy)-N-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-5-nitrobenzamido)-3-methylbutyl)(methyl)carbamate	[M+H] ⁺ calcd 670; found, 670
U18		2-(allyloxy)-N-((2R,3R)-3-(allyloxy)-4-(4-fluoro-N-methylphenylsulfonamido)-2-methylbutyl)-N-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-5-nitrobenzamide	[M+H] ⁺ calcd 714; found, 714
U19		N-((R)-3-(allyloxy)-4-(4-fluoro-N-methylphenylsulfonamido)butyl)-N-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-5-nitro-2-((S)-pent-4-en-2-yloxy)benzamide	[M+H] ⁺ calcd 728; found, 728

No.	Structure	Name	MS
U20		tert-butyl ((2R,3R)-2-(allyloxy)-4-(N-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-5-nitro-2-((S)-pent-4-en-2-yloxy)benzamido)-3-methylbutyl)carbamate	[M+H] ⁺ calcd 670; found, 670
U21		N-((2R,3R)-3-(allyloxy)-4-(4-fluoro-N-methylphenylsulfonamido)-2-methylbutyl)-N-((S)-1-(4-methoxybenzyloxy)propan-2-yl)-5-nitro-2-((R)-pent-4-en-2-yloxy)benzamide	[M+H] ⁺ calcd 742; found, 742

Boc deprotection of U12:

5

Synthesis of N-((2R,3R)-3-(allyloxy)-4-(4-fluoro-N-methylphenylsulfonamido)-2-methylbutyl)-2-(but-3-en-1-ylamino)-N-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-5-nitrobenzamide

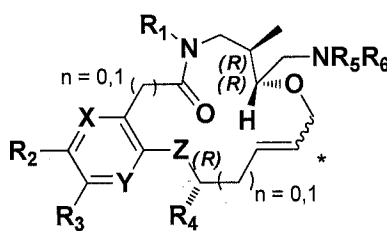
To a chilled (using ice bath) solution of U12 (180 mg, 0.218 mmol) in DCM (4353 μ l) under Nitrogen was added 2,6-dimethylpyridine (203 μ l, 1.741 mmol) followed by tert-butyldimethylsilyl trifluoromethanesulfonate (257 μ l, 1.088 mmol). The reaction was stirred at 0 °C for 25 min, then was stirred at room temperature. After 5h further 2,6-dimethylpyridine (100 μ L 0.857 mmol) and tert-butyldimethylsilyl trifluoromethanesulfonate (130 μ L 1.088 mmol) were added. After 6h, 2,6-Lutidine (0.2 mL) was added, then saturated ammonium chloride (5 mL) was added slowly. The aqueous component was extracted with DCM (3 x 35 mL) and the combined organic layers were washed with water and brine, dried over Na₂SO₄, filtered and the solvent evaporated. To a solution of the residue in THF (4.0 ml) was added pyridine hydrofluoride (48.7 μ l, 0.392 mmol) at room temperature. The reaction was stirred for 30 min and then diluted with saturated ammonium chloride and extracted with EtOAc (3 x 35 mL). The combined organics were washed with brine, dried (Na₂SO₄) and the solvent evaporated. The reaction was purified by column chromatography using DCM/Methanol to afford the desired product (130 mg, 82 %).

- ¹H NMR (300 MHz, CDCl₃) δ 8.10-7.98 (m, 2H), 7.82-7.67 (m, 2H), 7.25-7.07 (m, 4H), 6.86-6.71 (m, 2H), 6.51 (d, *J* = 9.5, 1H), 5.98 – 5.54 (m, 3H), 5.26 – 4.90 (m, 5H), 4.43-4.24 (s, 2H), 4.09-3.82 (m, 3H), 3.73 (s, 3H), 3.46 – 2.88 (m, 5H), 2.81-2.58 (m, 5H), 2.23-1.99 (m, 4H), 1.22 – 1.05 (m, 3H), 1.01 – 0.61 (m, 3H). MS calculated for C₃₇H₄₇FN₄O₈S [M+H]⁺: 727. Found: 727.

Ring-closing metathesis:

- Intermediates **V1-V22** were synthesized following the procedure previously reported in Marcaurelle, L. A.; Comer, E.; Dandapani, S.; Duvall, J. R.; Gerard, B.; Kesavan, S.; Lee, M. D, IV; Liu, H.; Lowe, J. T.; Marie, J.-C.; Mulrooney, C. A.; Pandya, B. A.; Rowley, A.; Ryba, T. D.; Suh, B.-C.; Wei, J.; Young, D. W.; Akella, L. B.; Ross, N. B.; Zhang, Y.-L.; Fass, D. M.; Reis, S. A.; Zhao, W.-N.; Haggarty, S. J.; Palmer, M.; Foley, M. A. *J. Am. Chem. Soc.* **2010**, *132*, 16962-16976.

Intermediate V:



No.	Structure	Name	MS
V1		tert-butyl methyl(((2S,8R,9R)-2,9,11-trimethyl-14-nitro-12-oxo-2,3,6,8,9,10,11,12-octahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)carbamate	[M+H] ⁺ calcd 492; found,492
V2		tert-butyl (((2S,8R,9R)-11-isopropyl-2,9-dimethyl-14-nitro-12-oxo-2,3,6,8,9,10,11,12-octahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)(methyl)carbamate	[M+H] ⁺ calcd 520; found,520
V3		tert-butyl (((2S,8R,9R)-11-(2-((4-methoxybenzyl)oxy)ethyl)-2,9-dimethyl-14-nitro-12-oxo-2,3,6,8,9,10,11,12-octahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)(methyl)carbamate	[M+H] ⁺ calcd 642; found,642

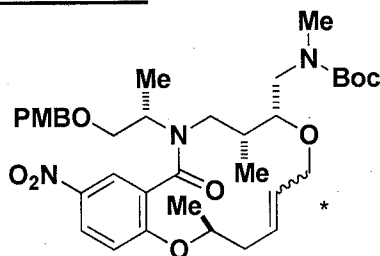
No.	Structure	Name	MS
V4		tert-butyl (((2S,8R,9R)-11-((S)-1-(tert-butoxy)propan-2-yl)-2,9-dimethyl-14-nitro-12-oxo-2,3,6,8,9,10,11,12-octahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)(methyl)carbamate	[M+H] ⁺ calcd 592; found, 592
V5		tert-butyl (((8R,9R,15S,E/Z)-6-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-8,15-dimethyl-5-oxo-5,6,7,8,9,11,14,15-octahydropyrido[2,3-b][1,9,5]dioxazacyclotetradecin-9-yl)methyl)(methyl)carbamate	[M+H] ⁺ calcd 612; found, 612
V6		tert-butyl (((2S,8R,9R,E/Z)-11-((R)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2,9-dimethyl-14-nitro-12-oxo-2,3,6,8,9,10,11,12-octahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)(methyl)carbamate	[M+H] ⁺ calcd 656; found, 656
V7		tert-butyl (((2S,8R,9R,E/Z)-14-fluoro-11-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2,9-dimethyl-12-oxo-2,3,6,8,9,10,11,12-octahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)(methyl)carbamate	[M+H] ⁺ calcd 629; found, 629
V8		tert-butyl (((2S,8R,9R,E/Z)-11-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2,9-dimethyl-12-oxo-15-(trifluoromethyl)-2,3,6,8,9,10,11,12-octahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)(methyl)carbamate	[M+H] ⁺ calcd 679; found, 679
V9		tert-butyl (((6S,12R,13R,E/Z)-15-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-6,13-dimethyl-16-oxo-6,7,10,12,13,14,15,16-octahydropyrido[3,2-b][1,9,5]dioxazacyclotetradecin-12-yl)methyl)(methyl)carbamate	[M+H] ⁺ calcd 612; found, 612
V10		tert-butyl (((2S,8S,9R,E/Z)-14-cyano-11-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2,9-dimethyl-12-oxo-2,3,6,8,9,10,11,12-octahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)(methyl)carbamate	[M+H] ⁺ calcd 636; found, 636

No.	Structure	Name	MS
V11		tert-butyl (((2S,8R,9R,E/Z)-11-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2,9-dimethyl-12-oxo-14-(trifluoromethyl)-2,3,6,8,9,10,11,12-octahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)(methyl)carbamate	[M+H] +calcd 679; found, 679
V12		4-fluoro-N-(((8R,9R,E)-11-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-9-methyl-15-nitro-12-oxo-3,6,8,9,10,11,12,13-octahydro-2H-benzo[h][1,10,5]dioxazacyclopentadecin-8-yl)methyl)-N-methylbenzenesulfonamide	[M+H] +calcd 714; found, 714
V13		4-fluoro-N-(((7R,8R,Z)-10-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-8-methyl-14-nitro-11-oxo-2,5,7,8,9,10,11,12-octahydrobenzo[h][1,10,5]dioxazacyclotetradecin-7-yl)methyl)-N-methylbenzenesulfonamide	[M+H] +calcd 700; found, 700
V14		4-fluoro-N-(((8R,9R,E)-11-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-9-methyl-14-nitro-12-oxo-2,3,6,8,9,10,11,12-octahydro-1H-benzo[g][1,5,9]oxadiazacyclotetradecin-8-yl)methyl)-N-methylbenzenesulfonamide	[M+H] +calcd 699; found, 699
V15		4-fluoro-N-(((6S,12R,13R,E)-15-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-6,13-dimethyl-16-oxo-6,7,10,12,13,14,15,16-octahydropyrazino[2,3-b][1,9,5]dioxazacyclotetradecin-12-yl)methyl)-N-methylbenzenesulfonamide	[M+H] +calcd 671; found, 671
V16		4-fluoro-N-(((4R,5R,Z)-2-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-4-methyl-15-nitro-1,1-dioxido-3,4,5,7,10,11-hexahydro-2H-benzo[b][1,9,4,5]dioxathiazacyclotetradecin-5-yl)methyl)-N-methylbenzenesulfonamide	[M+Na] ⁺ calcd 758; found, 758

No.	Structure	Name	MS
V17		4-fluoro-N-(((5S,11R,12R,E)-14-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-5,12-dimethyl-15-oxo-5,6,9,11,12,13,14,15-octahydrothieno[3,2-b][1,9,5]dioxazacyclotetradecin-11-yl)methyl)-N-methylbenzenesulfonamide	[M+Na] ⁺ calcd 675; found, 675
V18		4-fluoro-N-(((7R,8R,14S,Z)-5-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-1,7,14-trimethyl-4-oxo-4,5,6,7,8,10,13,14-octahydro-1H-pyrazolo[3,4-b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)-N-methylbenzenesulfonamide	[M+Na] ⁺ calcd 673; found, 673
V19		tert-butyl (((8R,9R)-11-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-9-methyl-14-nitro-12-oxo-2,3,6,8,9,10,11,12-octahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)(methyl)carbamate	[M+H] ⁺ calcd 642; found, 642
V20		4-fluoro-N-(((2S,8R)-11-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2-methyl-14-nitro-12-oxo-2,3,6,8,9,10,11,12-octahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)-N-methylbenzenesulfonamide	[M+H] ⁺ calcd 700; found, 700
V21		tert-butyl (((2S,8R,9R)-11-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2,9-dimethyl-14-nitro-12-oxo-2,3,6,8,9,10,11,12-octahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)carbamate	[M+H] ⁺ calcd 642; found, 642
V22		4-fluoro-N-(((2R,8R,9R)-11-((S)-1-((4-methoxybenzyloxy)propan-2-yl)-2,9-dimethyl-14-nitro-12-oxo-2,3,6,8,9,10,11,12-octahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)-N-methylbenzenesulfonamide	[M+H] ⁺ calcd 714; found, 714

*Mixture of *E* and *Z* isomers

Separation of the *E* and *Z* isomers after ring closing metathesis to prepare intermediates V23 *E/Z* and V24 *E/Z*:



- 5 The crude mixture of **V23** and **V24** was prepared and characterized as reported in: Marcaurelle, L. A.; Comer, E.; Dandapani, S.; Duvall, J. R.; Gerard, B.; Kesavan, S.; Lee, M. D, IV; Liu, H.; Lowe, J. T.; Marie, J.-C.; Mulrooney, C. A.; Pandya, B. A.; Rowley, A.; Ryba, T. D.; Suh, B.-C.; Wei, J.; Young, D. W.; Akella, L. B.; Ross, N. B.; Zhang, Y.-L.; Fass, D. M.; Reis, S. A.; Zhao, W.-N.; Haggarty, S. J.; Palmer, M.;
 10 Foley, M. A. *J. Am. Chem. Soc.* **2010**, *132*, 16962-16976.

The mixture of isomers was purified by silica gel chromatography using EtOAc in hexanes to yield two pure isomers, the earlier eluting product from the SiO₂ column will be labeled intermediate **V23** and the later eluting product intermediate **V24**.

15

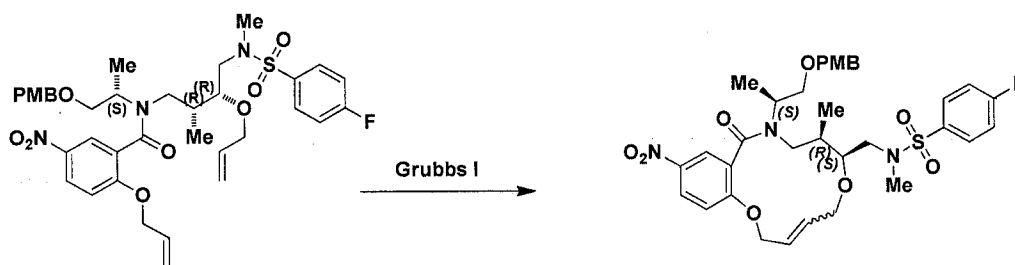
No.	Structure	Name	Mass
V23 <i>E/Z</i>		tert-butyl (((2 <i>S</i> ,8 <i>R</i> ,9 <i>R</i> , <i>E/Z</i>)-14-nitro-11-((<i>S</i>)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2,9-dimethyl-12-oxo-2,3,6,8,9,10,11,12-octahydrobenzo[<i>b</i>][1,9,5]dioxazacyclotetradecin-8-yl)methyl)(methyl)carbamate	[<i>M</i> + <i>H</i>] ⁺ calcd 656; found, 656
V24 <i>E/Z</i>		tert-butyl (((2 <i>S</i> ,8 <i>R</i> ,9 <i>R</i> , <i>E/Z</i>)-14-nitro-11-((<i>S</i>)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2,9-dimethyl-12-oxo-2,3,6,8,9,10,11,12-octahydrobenzo[<i>b</i>][1,9,5]dioxazacyclotetradecin-8-yl)methyl)(methyl)carbamate	[<i>M</i> + <i>H</i>] ⁺ calcd 656; found, 656

**E* or *Z* isomer

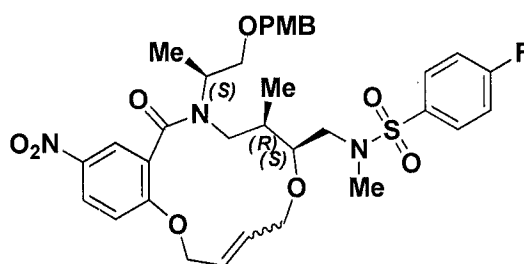
Alternative Ring Closing Metathesis for 13-membered analogue Intermediate V25:

20

- 80 -



Intermediate V25



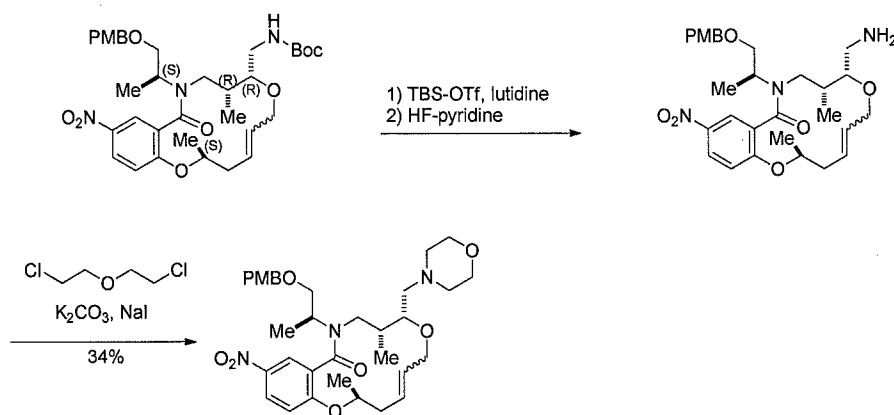
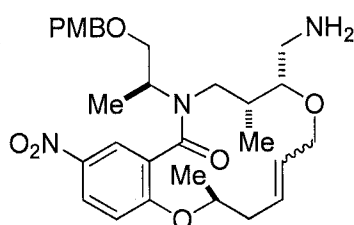
5

Synthesis of 4-fluoro-N-(((7S,8R)-10-(((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-8-methyl-13-nitro-11-oxo-5,7,8,9,10,11-hexahydro-2H-benzo[b][1,9,5]dioxaaazacyclotridecin-7-yl)methyl)-N-methylbenzenesulfonamide

- 10 To a solution of **U18** (690 mg, 0.967 mmol) in DCM (96.700 ml) Grubbs I catalyst (0.129 g, 0.153 mmol) was added and the reaction mixture was stirred at room temperature for 72 hours. Then the solvent was removed under pressure and the crude product was purified by silica gel chromatography using ethylacetate/hexanes to afford 433 mg of desired product (65% yield). ¹H NMR (300 MHz, CDCl₃) δ 8.29 – 8.04 (m, 1H), 7.85 – 7.71 (m, 2H), 7.25 – 7.08 (m, 4H), 7.04–6.95 (m, 1H), 6.94 – 6.80 (m, 3H), 6.08 – 5.70 (m, 2H), 4.72–4.24 (m, 4H), 4.15 – 3.97 (m, 1H), 3.93 – 3.56 (m, 5H), 3.47–3.25 (m, 4H), 3.24–3.08 (m, 2H), 2.89 – 2.44 (m, 6H), 1.93 – 1.46 (m, 1H), 1.28 – 1.05 (m, 3H), 1.00 – 0.77 (m, 3H). MS (ESI) calcd for C₃₄H₄₀FN₃O₉S [M + H]⁺: 686. Found: 686.
- 15
- 20

Synthesis of Intermediate X from Intermediate V21

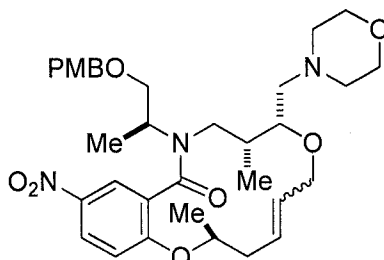
- 81 -

**Intermediate W:**

5

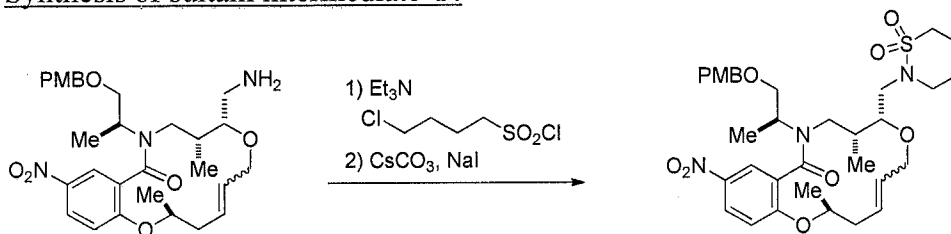
(2*S*,8*R*,9*R*)-8-(aminomethyl)-11-((*S*)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2,9-dimethyl-14-nitro-2,3,8,9,10,11-hexahydrobenzo[*b*][1,9,5]dioxazacyclotetradecin-12(6*H*)-one

- 10 To a solution of *tert*-butyl (((2*S*,8*R*,9*R*)-11-((*S*)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2,9-dimethyl-14-nitro-12-oxo-2,3,6,8,9,10,11,12-octahydrobenzo[*b*][1,9,5]dioxazacyclotetradecin-8-yl)methyl)carbamate (0.232 g, 0.362 mmol) in dry CH₂Cl₂ (3.6 mL) under N₂ and chilled in an ice-H₂O bath was added 2,6-dimethylpyridine (0.168 mL, 1.45 mmol) followed by *tert*-
- 15 butyldimethylsilyl trifluoromethanesulfonate (0.21 mL, 0.90 mmol). The reaction mixture was stirred in the ice-H₂O bath 30 min then allowed to warm to rt and stirred 3 h. Then additional 2,6-dimethylpyridine (0.168 mL, 1.45 mmol) was added and the reaction quenched with sat. aq. NaHCO₃. The aqueous phase was extracted with CH₂Cl₂ and the organic phase was washed with H₂O, dried (Na₂SO₄) and
- 20 solvent evaporated. The residue was dissolved in THF (3.6 mL) in a 81eflon bottle and to this was added pyridine hydrofluoride (0.045 mL, 0.36 mmol). The solution was stirred 20 min then quenched with sat. NaHCO₃ and the aqueous phase was extracted with EtOAc. The organics were washed with H₂O, brine, dried (Na₂SO₄) and the solvent evaporated. The residue was azeotroped with toluene 3X and the
- 25 solvent removed under vacuum. The residue was carried on to the next step without further purification. ¹H NMR (300 MHz, CDCl₃) δ 8.24-8.04 (m, 2H), 7.26 – 7.12 (m, 2H), 6.94 – 6.82 (m, 3H), 5.60 – 5.41 (m, 2H), 4.80 – 4.36 (m, 3H), 4.17 – 3.85 (m, 2H), 3.77 (s, 3H), 3.74 – 3.45 (m, 3H), 3.44 – 3.06 (m, 3H), 2.86-2.66 (m, 1H), 2.63 – 2.35 (m, 2H), 2.31 – 1.78 (m, 2H), 1.41 – 1.20 (m, 3H), 1.07 (d, *J* = 6.6 Hz, 3H), 0.93 – 0.78 (m, 3H). MS calculated for C₂₉H₄₀N₃O₇ [M+H]⁺: 542. Found: 542.
- 30

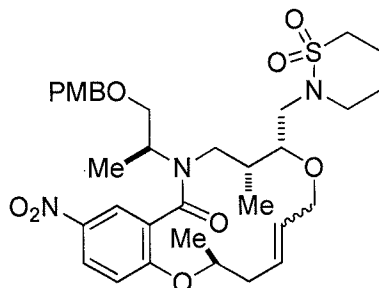
Intermediate X:

(2*S*,8*R*,9*R*)-11-((*S*)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2,9-dimethyl-8-(morpholinomethyl)-14-nitro-2,3,8,9,10,11-hexahydrobenzo[*b*][1,9,5]dioxazacyclotetradecin-12(6*H*)-one

- 5 To a mixture of (2*S*,8*R*,9*R*)-8-(aminomethyl)-11-((*S*)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2,9-dimethyl-14-nitro-2,3,8,9,10,11-hexahydrobenzo[*b*][1,9,5]dioxazacyclotetradecin-12(6*H*)-one (0.0383 g, 0.071 mmol), K₂CO₃ (0.029 g, 0.21 mmol), and NaI (5.3 mg, 0.035 mmol) in DMF (0.71 mL) under Ar was added 1-chloro-2-(2-chloroethoxy)ethane (0.012 mL, 0.11 mmol). The mixture was stirred in a 60 °C oil bath for 96h. The reaction mixture was cooled and diluted with H₂O and EtOAc. The aqueous phase was washed with EtOAc and the organic phase was washed with H₂O, dried (Na₂SO₄) and the solvent evaporated.
- 15 Purification was accomplished by SiO₂ chromatography to yield 14.8 mg (34%) of pure product. ¹H NMR (300 MHz, CDCl₃) δ 8.25 – 8.05 (m, 2H), 7.26 – 7.18 (m, 2H), 6.95-6.84 (m, 3H), 5.62-5.35 (m, 2H), 4.77 – 4.40 (m, 3H), 4.22 – 4.09 (m, 1H), 4.04-3.90 (m, 2H), 3.81(s, 3H), 3.82 – 3.34 (m, 7H), 2.75 – 2.20 (m, 8H), 2.10-1.71 (m, 1H), 1.42 – 1.31 (m, 3H), 1.07 (dd, *J* = 6.5, 3.5 Hz, 3H), 0.89 (dd, *J* = 7.1, 3.7 Hz, 3H). MS calculated for C₃₃H₄₆N₃O₈ [M+H]⁺: 612. Found: 612.
- 20

Synthesis of sultam intermediate Y:

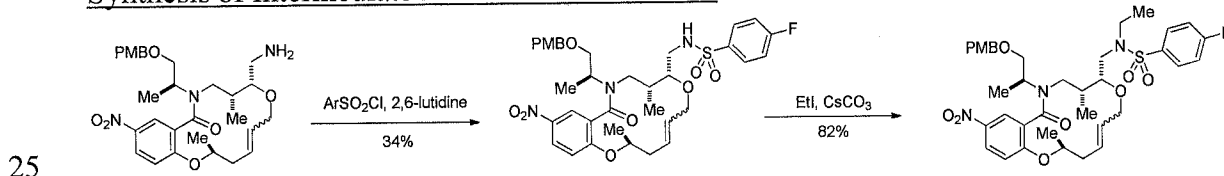
25 **Intermediate Y:**



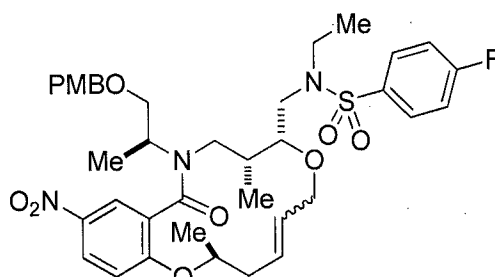
(2*S*,8*R*,9*R*)-8-((1,1-dioxido-1,2-thiazinan-2-yl)methyl)-11-((*S*)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2,9-dimethyl-14-nitro-2,3,8,9,10,11-hexahydrobenzo[*b*][1,9,5]dioxazacyclotetradecin-12(6*H*)-one

To a chilled (0 °C) solution of (2*S*,8*R*,9*R*)-8-(aminomethyl)-11-((*S*)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2,9-dimethyl-14-nitro-2,3,8,9,10,11-hexahydrobenzo[*b*][1,9,5]dioxazacyclotetradecin-12(6*H*)-one (0.060 g, 0.11 mmol) in CH₂Cl₂ (1.1 mL) was added Et₃N (0.046 mL, 0.33 mmol) and 4-chlorobutane-1-sulfonyl chloride (0.025 g, 0.13 mmol). The reaction mixture was stirred 1 h at 0 °C, then warmed to rt and stirred for 16 h. The solvent was evaporated and the residue was dissolved in acetonitrile (1.1 mL), then CsCO₃ (0.108 g, 0.333 mmol) and NaI (8.3 mg, 0.056 mmol) were added, and the reaction mixture was stirred in a 70 °C oil bath for 24 h. The mixture was then cooled to rt and the solvent evaporated. The residue was diluted in EtOAc and H₂O, and the phases partitioned. The aqueous phase was extracted with EtOAc, the combined organic layers were dried over Na₂SO₄ and the solvent evaporated. Purification was accomplished with SiO₂ chromatography to yield 54 mg (74 %) of pure product. ¹H NMR (300 MHz, CDCl₃) δ 8.22 (dd, *J* = 9.2, 2.7 Hz, 1H), 8.10 (dd, *J* = 4.8, 2.8 Hz, 1H), 7.25 – 7.20 (m, 2H), 6.96 – 6.85 (m, 3H), 5.68 – 5.36 (m, 2H), 4.76 – 4.65 (m, 1H), 4.59 – 4.41 (m, 2H), 4.07–3.87 (m, 1H), 3.79 (s, 3H), 3.78 – 3.35 (m, 6H), 3.26 – 3.00 (m, 2H), 2.92 – 2.39 (m, 4H), 2.31 – 1.90 (m, 4H), 1.79 – 1.45 (m, 2H), 1.39 – 1.32 (m, 3H), 1.10–1.04 (m, 3H), 0.95 – 0.85 (m, 3H). MS calculated for C₃₃H₄₆N₃O₉S [M+H]⁺: 660. Found: 660.

Synthesis of Intermediate Z from Intermediate W



Intermediate Z:



30 ***N*-ethyl-4-fluoro-*N*-(((2*S*,8*R*,9*R*)-11-((*S*)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2,9-dimethyl-14-nitro-12-oxo-2,3,6,8,9,10,11,12-octahydrobenzo[*b*][1,9,5]dioxazacyclotetradecin-8-yl)methyl)benzenesulfonamide**

To a solution of (2*S*,8*R*,9*R*)-8-(aminomethyl)-11-((*S*)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2,9-dimethyl-14-nitro-2,3,8,9,10,11-hexahydrobenzo[*b*][1,9,5]dioxazacyclotetradecin-12(6*H*)-one (0.211 g, 0.390 mmol) in dry CH₂Cl₂ (3.9 mL) under N₂ was added 2,6-lutidine (0.136 mL, 1.17 mmol) followed by 4-fluorobenzene-1-sulfonyl chloride (0.152 g, 0.779 mmol).

35

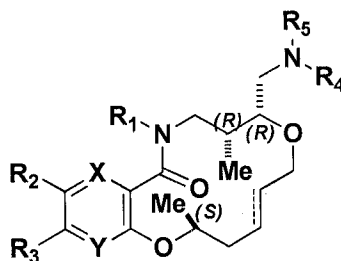
The reaction mixture was stirred overnight at rt. Then it was diluted with CH₂Cl₂ and washed with H₂O. The aqueous phase was extracted with CH₂Cl₂, and the combined organics were washed with H₂O, dried (Na₂SO₄) and the solvent evaporated. Purification was accomplished by SiO₂ chromatography to yield 103 mg (34%) of pure product.

To a solution of this product (0.103 g, 0.147 mmol) and iodoethane (0.018 mL, 0.22 mmol) in dry DMF (0.736 mL) under N₂ was added CsCO₃ (0.096 g, 0.29 mmol). The reaction mixture was stirred for 2 h at rt, then diluted with EtOAc and H₂O, the phases were partitioned and the organic phase was washed with H₂O, brine, dried (Na₂SO₄) and the solvent evaporated. Purification was accomplished by SiO₂ chromatography to yield 82 mg (88%) of pure product. ¹H NMR (300 MHz, CDCl₃) δ 8.24 – 8.15 (m, 1H), 8.10 (dd, *J* = 8.4, 2.8 Hz, 1H), 7.92 – 7.85 (m, 2H), 7.28 – 7.16 (m, 2H), 7.09 (ddd, *J* = 8.7, 6.3, 3.0 Hz, 2H), 6.94 – 6.80 (m, 3H), 5.72–4.98 (m, 2H), 4.93 – 4.64 (m, 1H), 4.50 – 4.39 (m, 2H), 4.04–3.95 (m, 1H), 3.79 (s, 3H), 3.78–3.04 (m, 10H), 2.72 (d, *J* = 14.0 Hz, 1H), 2.61 – 2.09 (m, 1H), 2.04 – 1.88 (m, 2H), 1.35 – 1.29 (m, 3H), 1.28 – 1.21 (m, 3H), 1.13 – 1.00 (m, 3H), 0.99 – 0.77 (m, 3H). MS calculated for C₃₇H₄₇N₃O₉S [M+H]⁺: 728. Found: 728.

Reduction of the nitro and olefin groups by catalytic hydrogenation:

The following intermediates AA1-AA18 were synthesized following the procedure previously reported in Marcaurelle, L. A.; Comer, E.; Dandapani, S.; Duvall, J. R.; Gerard, B.; Kesavan, S.; Lee, M. D, IV; Liu, H.; Lowe, J. T.; Marie, J.-C.; Mulrooney, C. A.; Pandya, B. A.; Rowley, A.; Ryba, T. D.; Suh, B.-C.; Wei, J.; Young, D. W.; Akella, L. B.; Ross, N. B.; Zhang, Y.-L.; Fass, D. M.; Reis, S. A.; Zhao, W.-N.; Haggarty, S. J.; Palmer, M.; Foley, M. A. *J. Am. Chem. Soc.* **2010**, 132, 16962-16976.

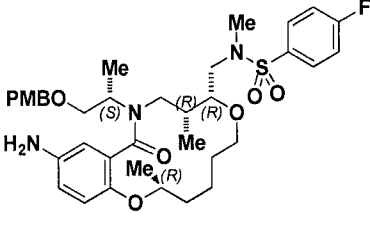
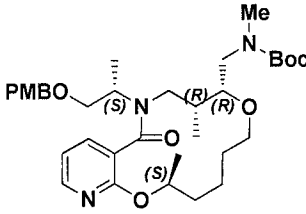
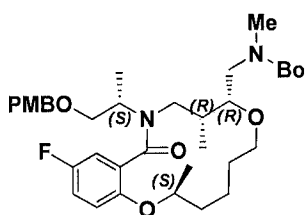
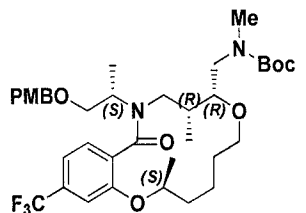
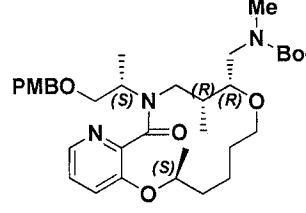
Intermediates AA and 1:



No.	Structure	Name	MS
AA1		tert-butyl (((2S,8R,9R)-14-amino-2,9,11-trimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)(methyl)carbamate	[M+H] ⁺ calcd 464; found, 464

No.	Structure	Name	MS
AA2		tert-butyl (((2S,8R,9R)-14-amino-11-isopropyl-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)(methyl)carbamate	[M+H] ⁺ calcd 492; found, 492
AA3		tert-butyl (((2S,8R,9R)-14-amino-11-(2-((4-methoxybenzyl)oxy)ethyl)-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)(methyl)carbamate	[M+H] ⁺ calcd 614; found, 614
AA4		tert-butyl (((2S,8R,9R)-14-amino-11-((S)-1-(tert-butoxy)propan-2-yl)-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)(methyl)carbamate	[M+H] ⁺ calcd 564; found, 564
AA5		tert-butyl (((2S,8R,9R)-14-amino-11-((R)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)(methyl)carbamate	[M+H] ⁺ calcd 628; found, 628
AA6		4-fluoro-N-(((4R,5R)-2-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-4-methyl-15-nitro-1,1-dioxido-3,4,5,7,8,9,10,11-octahydro-2H-benzo[b][1,9,4,5]dioxathiazacyclotetradecin-5-yl)methyl)-N-methylbenzenesulfonamide	[M+H] ⁺ calcd 708; found, 708
AA7		N-(((2S,8R,9R)-14-amino-11-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)-4-fluoro-N-methylbenzenesulfonamide	[M+H] ⁺ calcd 686; found, 686

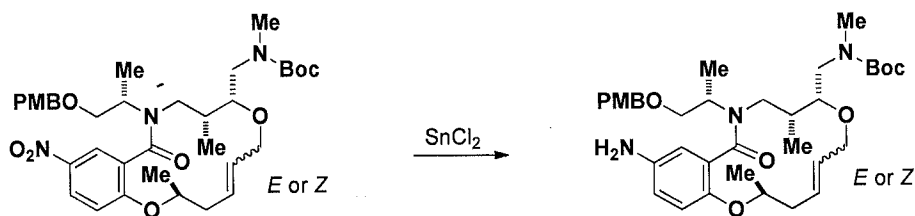
No.	Structure	Name	MS
1		4-fluoro-N-(((7R,8R,14S)-5-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-1,7,14-trimethyl-4-oxo-4,5,6,7,8,10,11,12,13,14-decahydro-1H-pyrazolo[3,4-b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)-N-methylbenzenesulfonamide	[M+H] ⁺ calcd 675; found, 675
AA8		tert-butyl (((8R,9R)-14-amino-11-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-9-methyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)(methyl)carbamate	[M+H] ⁺ calcd 614; found, 614
AA9		N-(((2S,8R)-14-amino-11-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2-methyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)-4-fluoro-N-methylbenzenesulfonamide	[M+H] ⁺ calcd 672; found, 672
AA10		((2S,8R,9R)-14-amino-11-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2,9-dimethyl-8-(morpholinomethyl)-3,4,5,6,8,9,10,11-octahydrobenzo[b][1,9,5]dioxazacyclotetradecin-12(2H)-one	[M+H] ⁺ calcd 584; found, 584
AA11		N-(((2S,8R,9R)-14-amino-11-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)-N-ethyl-4-fluorobenzene sulfonamide	[M+H] ⁺ calcd 700; found, 700

No.	Structure	Name	MS
AA12		N-(((2R,8R,9R)-14-amino-11-((S)-1-(4-methoxybenzyloxy)propan-2-yl)-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)-4-fluoro-N-methylbenzenesulfonamide	[M+H] ⁺ calcd 686; found, 686
AA13		tert-butyl (((8R,9R,15S)-6-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-8,15-dimethyl-5-oxo-5,6,7,8,9,11,12,13,14,15-decahydropyrido[2,3-b][1,9,5]dioxazacyclotetradecin-9-yl)methyl)(methyl)carbamate	[M+H] ⁺ calcd 614; found, 614
AA14		tert-butyl (((2S,8R,9R)-14-fluoro-11-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)(methyl)carbamate	[M+H] ⁺ calcd 631; found, 631
AA15		tert-butyl (((2S,8R,9R)-11-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2,9-dimethyl-12-oxo-15-(trifluoromethyl)-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)(methyl)carbamate	[M+H] ⁺ calcd 681; found, 681
AA16		tert-butyl (((6S,12R,13R)-15-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-6,13-dimethyl-16-oxo-6,7,8,9,10,12,13,14,15,16-decahydropyrido[3,2-b][1,9,5]dioxazacyclotetradeci	[M+H] ⁺ calcd 614; found, 614

No.	Structure	Name	MS
		n-12-yl)methyl)(methyl)carbamate	
AA17		tert-butyl (((2S,8S,9R)-14-cyano-11-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)(methyl)carbamate	[M+H] ⁺ calcd 638; found, 638
AA18		tert-butyl (((2S,8R,9R)-11-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2,9-dimethyl-12-oxo-14-(trifluoromethyl)-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)(methyl)carbamate	[M+H] ⁺ calcd 681; found, 681
AA19		tert-butyl (((2S,8R,9R)-14-amino-11-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)(methyl)carbamate	[M+H] ⁺ calcd 628; found, 628

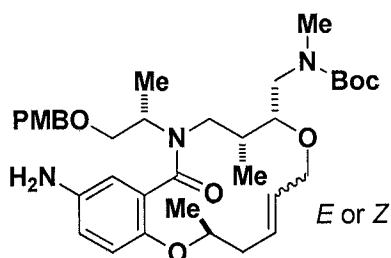
Selective reduction of –NO₂ in presence of olefin to provide intermediates BB1-BB3:

5



Intermediate BB1 :

- 89 -



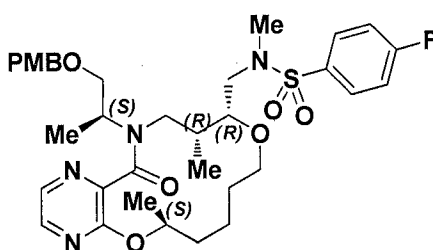
5 (tert-butyl (((2S,8R,9R,E/Z)-14-amino-11-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2,9-dimethyl-12-oxo-2,3,6,8,9,10,11,12-octahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)(methyl)carbamate) (BB1)

To a solution of nitro compound intermediate **V23** (0.1928 g, 0.294 mmol) in methanol (1.470 ml) under N₂ atmosphere was added tin(II) chloride dihydrate (0.332 g, 1.470 mmol) at room temperature. The resulting mixture was stirred for 20 h. The reaction was diluted with EtOAc and washed with 2N KOH aqueous solution, then with water (2 X), brine, finally dried over Na₂SO₄ and evaporated to dryness. This material was chromatographed on silica, using methanol / dichloromethane to give the desired product (0.121 g, 66%) as colorless resin. ¹H NMR (300 MHz, CDCl₃) δ 7.25 (d, 2H), 6.88 (d, 2H), 6.74 – 6.40 (m, 3H), 5.59 – 5.23 (m, 1H), 4.47 (s, 2H), 4.28 (m, 1H), 3.99 (s, 2H), 3.92 – 3.66 (m, 6H), 3.56 (m, 2H), 3.43 (s, 2H), 3.09 (m, 1H), 2.89 (m, 1H), 2.77 (m, 3H), 2.44 (m, 1H), 1.97 (m, 2H), 1.60 (s, 4H), 1.45 (m, 9H), 1.26 (m, 3H), 1.05 (d, 2H), 0.92 (m, 2H). MS calculated for C₃₅H₅₁N₃O₇ : [M+H]⁺ 626. Found: 626.

The following intermediate was prepared from this method starting with intermediate **V24**:

No.	Structure	Name	Mass
BB2 <i>E/Z</i>		tert-butyl (((2S,8R,9R,E/Z)-14-amino-11-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2,9-dimethyl-12-oxo-2,3,6,8,9,10,11,12-octahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)(methyl)carbamate	[M+H] ⁺ calcd 626; found, 626

25 Alternative reduction of the olefin groups by catalytic hydrogenation:

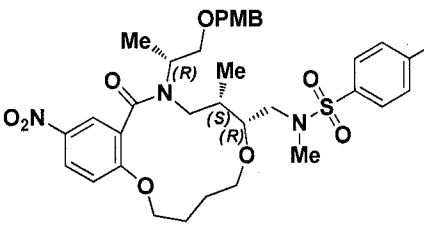
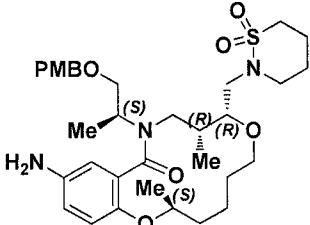


- 90 -

Compound 2:

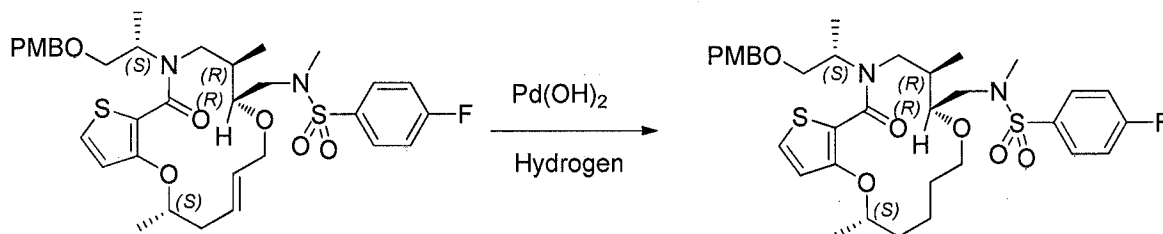
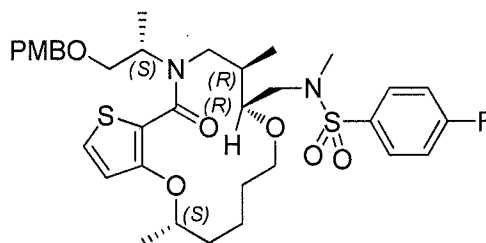
- Synthesis of 4-fluoro-N-(((6S,12R,13R)-15-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-6,13-dimethyl-16-oxo-6,7,8,9,10,12,13,14,15,16-decahydropyrazino[2,3-b][1,9,5]dioxazacyclotetradecin-12-yl)methyl)-N-methylbenzenesulfonamide**
- To a solution of V15 (35 mg, 0.052 mmol) in degassed THF (Volume: 522 μ l) and tertbutanol (Volume: 522 μ l) was added wilkinson's catalyst (19.31 mg, 2.10 μ mol).
- The reaction mixture was degassed and filled with Hydrogen using a Hydrogen balloon. The resulting mixture was stirred for 22 h. This material was evaporated to dryness and chromatographed on silica, using methanol / dichloromethane to give the desired product (0.022 g, 63%). ^1H NMR (300 MHz, CDCl_3) ^1H NMR (300 MHz, CDCl_3) δ 8.00-7.93 (m, 2H), 7.82 – 7.65 (m, 2H), 7.23 – 7.03 (m, 4H), 6.80 (d, J = 8.6 Hz, 2H), 5.16 (m, 1H), 4.46 – 4.23 (m, 2H), 4.08– 3.77 (m, 2H), 3.74 (s, 4H), 3.62 – 3.26 (m, 5H), 2.78 (s, 3H), 2.74-2.51 (m, 3H), 2.25-2.06 (m, 2H), 1.78 – 1.42 (m, 4H), 1.39 – 1.16 (m, 3H), 1.05 (d, J = 6.5 Hz, 3H), 0.94 – 0.58 (m, 3H). MS (ESI) calcd for $\text{C}_{34}\text{H}_{45}\text{FN}_4\text{O}_7\text{S}$ $[\text{M} + \text{H}]^+$: 673. Found: 673.

- The following intermediates were prepared from this method starting with intermediates V25 and Y:

No.	Structure	Name	Mass
AA20		4-fluoro-N-(((7R,8S)-10-((R)-1-((4-methoxybenzyl)oxy)propan-2-yl)-8-methyl-13-nitro-11-oxo-3,4,5,7,8,9,10,11-octahydro-2H-benzo[b][1,9,5]dioxazacyclotridecin-7-yl)methyl)-N-methylbenzenesulfonamide	$[\text{M} + \text{H}]^+$ calcd 688; found, 688
AA21		(2S,8R,9R)-8-((1,1-dioxido-1,2-thiazinan-2-yl)methyl)-11-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2,9-dimethyl-14-nitro-3,4,5,6,8,9,10,11-octahydrobenzo[b][1,9,5]dioxazacyclotetradecin-12(2H)-one	$[\text{M} + \text{H}]^+$ calcd 662; found, 662

Alternative reduction of the olefin groups by catalytic hydrogenation:

- 91 -

**Compound 3**

5

Synthesis of 4-fluoro-N-(((5S,11R,12R)-14-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-5,12-dimethyl-15-oxo-5,6,7,8,9,11,12,13,14,15-decahydrothieno[3,2-b][1,9,5]dioxazacyclotetradecin-11-yl)methyl)-N-methylbenzenesulfonamide

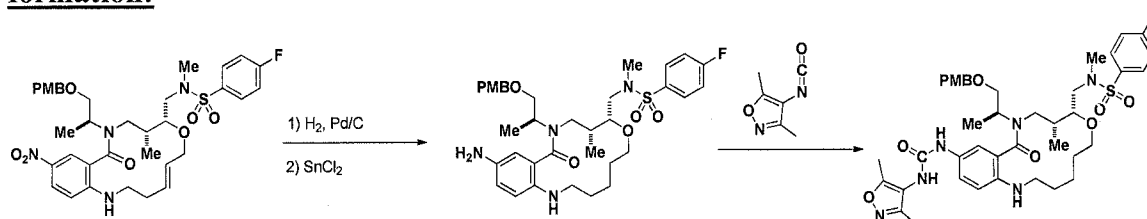
10

To a solution of V17 (0.053 g, 0.079 mmol) in MeOH (1.571 ml) at room temperature was added dihydroxypalladium (5.51 mg, 7.85 μ mol). The reaction was placed under a hydrogen gas atmosphere using a hydrogen balloon, and stirred for 10h. This material was evaporated to dryness and chromatographed on silica, using ethylacetate hexane to give the desired product (0.012 g, 60%) as colorless resin. ^1H NMR (300 MHz, CDCl_3) δ 7.81-7.64 (m, 2H), 7.27 – 6.93 (m, 5H), 6.84 – 6.76 (m, 2H), 6.64 – 6.55 (m, 1H), 4.40 (s, 3H), 4.30 – 3.94 (m, 2H), 3.74 (s, 3H), 3.62 – 3.43 (m, 4H), 3.39-3.20 (m, 2H), 3.01-2.85 (m, 1H), 2.80 – 2.57 (m, 3H), 2.05 – 1.73 (m, 2H), 1.69-1.51 (s, 2H), 1.48-1.27 (m, 3H), 1.33 – 1.15 (m, 4H), 1.05 (d, J = 6.6, 3H), 0.90 – 0.60 (m, 3H). MS (ESI) calcd for $\text{C}_{34}\text{H}_{45}\text{FN}_2\text{O}_7\text{S}_2$ $[\text{M} + \text{H}]^+$: 677. Found: 677.

15

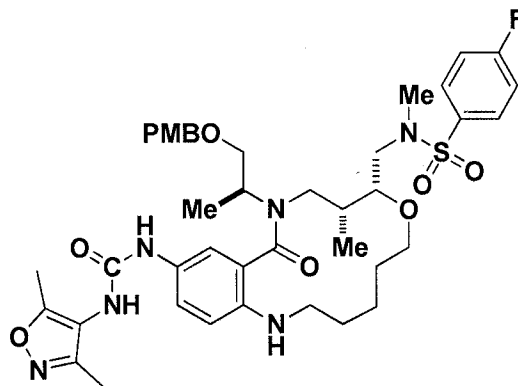
20

Alternative reduction of the Nitro and olefin groups followed by Urea formation:



25

Compound 4:

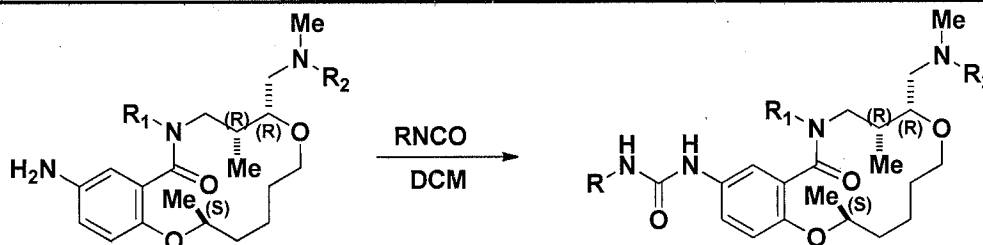


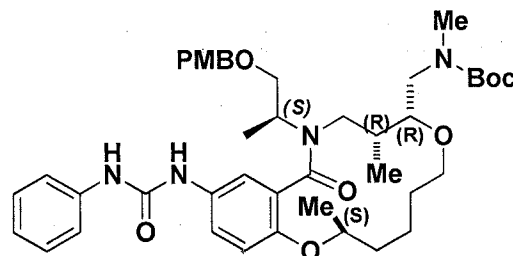
Synthesis of N-(((8R,9R)-14-(3-(3,5-dimethylisoxazol-4-yl)ureido)-11-((S)-1-(4-methoxybenzyl)oxy)propan-2-yl)-9-methyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1H-benzo[g][1,5,9]oxadiazacyclotetradecin-8-yl)methyl)-4-fluoro-N-methylbenzenesulfonamide

To a solution of V14 (30 mg, 0.043 mmol) in ethanol (429 μ l) was added 10% palladium on carbon (4.57 mg, 4.29 μ mol). The reaction mixture was degassed and back filled with a hydrogen balloon. The reaction was stirred at room temp for 16 h.

The reaction mixture was filtered through celite washing with dichloromethane and crude nitro material was carried forward to next step. To a solution of a portion of this crude material (7 mg, 9.99 μ mol) in Ethanol (100 μ l) was added Tin (II) chloride dihydrate (11.27 mg, 0.050 mmol) and the reaction was stirred at room temp. After 14h further Tin (II) chloride dihydrate (11.27 mg, 0.050 mmol) was added. After 22 h a sodium bicarbonate solution (300 μ l) was added and the reaction mixture was concentrated to remove Ethanol. The material was extracted with ethylacetate (2 x 10 mL). The combined organic layer was washed with water (1 mL), concentrated and the crude material was carried forward to next step. To a solution of this crude material (6.7 mg, 9.99 μ mol) in dry DCM (Volume: 100 μ l) under nitrogen was added 4-isocyanato-3,5-dimethylisoxazole (1.122 μ l, 9.99 μ mol). The reaction mixture was stirred for 16h. This material was evaporated to dryness and chromatographed on silica, using methanol / dichloromethane to give the desired product (4 mg, 50%). ¹H NMR (500 MHz, CDCl₃) 7.82-7.57 (m, 3H), 7.32-7.06 (m, 6H), 6.84-6.72 (m, 2H), 4.57-4.26 (m, 3H), 4.22 – 3.95 (m, 1H), 3.82 – 3.76 (m, 1H), 3.71 (s, 3H), 3.64 – 3.50 (m, 2H), 3.29 – 2.93 (m, 6H), 2.88-2.66 (m, 3H), 2.27 (s, 3H), 2.19-2.04 (m, 4H), 1.63-1.41 (m, 6H), 1.39–1.26 (m, 4H), 1.24-0.86 (m, 3H). MS (ESI) calcd for C₄₁H₅₃FN₆O₈S [M + H]⁺: 808. Found: 809.

Aryl urea formation to provide intermediates CC1-CC9 and Examples 5-13:



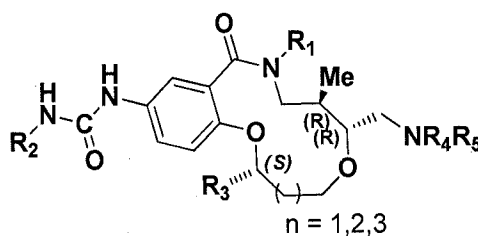
Intermediate CC1:

5 **tert-butyl (((2S,8R,9R)-11-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2,9-dimethyl-12-oxo-14-(3-phenylureido)-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)(methyl)carbamate (CC1)**

10 To a solution of tert-butyl (((2S,8R,9R)-14-amino-11-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)(methyl)carbamate **AA19** (570 mg, 0.908 mmol) in DCM (9.08 ml) under N₂ was added phenyl isocyanate (0.198 ml, 1.816 mmol). The reaction was stirred for 16h. The crude reaction mixture was evaporated under reduced pressure and purified by column chromatography using Ethylacetate/hexane to afford the desired product (568 mg, 84%) ¹HNMR (300 MHz, CDCl₃) δ 8.32–7.74 (m, 1H), 7.72–7.56 (m, 1H), 7.54–7.41 (m, 2H), 7.36–7.17 (m, 5H), 7.08–6.64 (m, 2H), 6.79–6.59 (m, 1H), 4.70–4.25 (m, 3H), 4.24–4.03 (m, 2H), 4.03–3.88 (m, 1H), 3.88–3.71 (m, 3H), 3.71–3.56 (m, 2H), 3.54–3.21 (m, 3H), 3.21–2.66 (m, 5H), 1.94–1.72 (m, 1H), 1.72–1.55 (m, 3H), 1.55–1.31 (m, 12H), 1.33–0.99 (m, 8H), 0.96–0.86 (m, 1H), 0.83–0.65 (m, 2H). MS (ESI) calcd for C₄₂H₅₈N₄O₈ [M + H]⁺: 747. Found: 747.

20

The following intermediates **CC2-CC9** and **Examples 6-14** were prepared from this method:



25

No.	Structure	Name	MS
5		tert-butyl methyl(((2S,8R,9R)-2,9,11-trimethyl-12-oxo-14-(3-phenylureido)-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)carbamate	[M+H] ⁺ calcd 583; found, 583

No.	Structure	Name	MS
CC2		tert-butyl (((2S,8R,9R)-11-isopropyl-2,9-dimethyl-12-oxo-14-(3-phenylureido)-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl(methyl)carbamate	[M+H] ⁺ calcd 611; found, 611
CC3		tert-butyl (((2S,8R,9R)-11-(2-((4-methoxybenzyl)oxy)ethyl)-2,9-dimethyl-12-oxo-14-(3-phenylureido)-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl(methyl)carbamate	[M+H] ⁺ calcd 733; found, 733
CC4		tert-butyl (((2S,8R,9R)-11-(1-(tert-butoxy)propan-2-yl)-2,9-dimethyl-12-oxo-14-(3-phenylureido)-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl(methyl)carbamate	[M+H] ⁺ calcd 683; found, 683
CC5		tert-butyl (((2S,8R,9R)-11-(1-(4-methoxybenzyl)oxy)propan-2-yl)-2,9-dimethyl-12-oxo-14-(3-phenylureido)-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl(methyl)carbamate	[M+H] ⁺ calcd 747; found, 747
CC6		tert-butyl (((2S,8R,9R,E/Z)-11-(1-(4-methoxybenzyl)oxy)propan-2-yl)-2,9-dimethyl-12-oxo-14-(3-phenylureido)-2,3,6,8,9,10,11,12-octahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl(methyl)carbamate	[M+H] ⁺ calcd 745; found, 745
CC7		tert-butyl (((2S,7R,8R,E/Z)-10-(1-(4-methoxybenzyl)oxy)propan-2-yl)-2,8-dimethyl-11-oxo-13-(3-phenylureido)-3,7,8,9,10,11-hexahydro-2H-benzo[b][1,9,5]dioxazacyclotr	[M+H] ⁺ calcd 745; found, 745

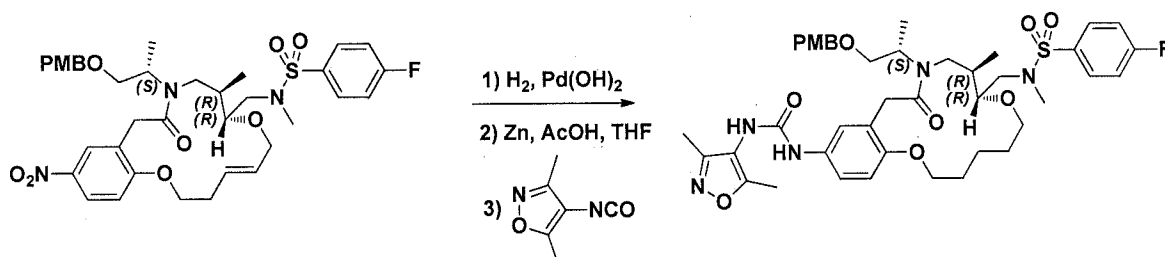
No.	Structure	Name	MS
		idecin-7-yl)methyl)(methyl)carbamate	
CC8		tert-butyl (((8R,9R)-14-(3-(3,5-dimethylisoxazol-4-yl)ureido)-11-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-9-methyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)(methyl)carbamate	[M+H] ⁺ calcd 752; found, 752
6		1-(3,5-dimethylisoxazol-4-yl)-3-((2S,8R,9R)-11-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2,9-dimethyl-8-(morpholinomethyl)-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-14-yl)urea	[M+H] ⁺ calcd 722; found, 722
7		N-(((2S,8R,9R)-14-(3-(3,5-dimethylisoxazol-4-yl)ureido)-11-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)-N-ethyl-4-fluorobenzenesulfonamide	[M+H] ⁺ calcd 838; found, 838
8		tert-butyl (((2S,8R,9R)-14-(3-(3,5-dimethylisoxazol-4-yl)ureido)-11-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)carbamate	[M+H] ⁺ calcd 752; found, 752

No.	Structure	Name	MS
CC9		tert-butyl (((2S,8R,9R)-14-(3-(3,5-dimethylisoxazol-4-yl)ureido)-11-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)(methyl)carbamate	[M+H] ⁺ calcd 765; found, 765
9		N-(((2R,8R,9R)-14-(3-(3,5-dimethylisoxazol-4-yl)ureido)-11-((S)-1-(4-methoxybenzyloxy)propan-2-yl)-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)-4-fluoro-N-methylbenzenesulfonamide	[M+H] ⁺ calcd 824; found, 824
10		N-(((4R,5R)-15-(3-(3,5-dimethylisoxazol-4-yl)ureido)-2-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-4-methyl-1,1-dioxido-3,4,5,7,8,9,10,11-octahydro-2H-benzo[b][1,9,4,5]dioxathiazacyclotetradecin-5-yl)methyl)-4-fluoro-N-methylbenzenesulfonamide	[M+H] ⁺ calcd 846; found, 846
11		N-(((6R,7R)-12-(3-(3,5-dimethylisoxazol-4-yl)ureido)-9-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-7-methyl-10-oxo-2,3,4,6,7,8,9,10-octahydrobenzo[f][1,5,9]dioxazacyclododecin-6-yl)methyl)-4-fluoro-N-methylbenzenesulfonamide	[M+H] ⁺ calcd 782; found, 782
12		N-(((7R,8S)-13-(3-(3,5-dimethylisoxazol-4-yl)ureido)-10-((R)-1-((4-methoxybenzyl)oxy)propan-2-yl)-8-methyl-11-oxo-3,4,5,7,8,9,10,11-octahydro-2H-benzo[b][1,9,5]dioxazacyclotridecin-7-yl)methyl)-4-fluoro-N-methylbenzenesulfonamide	[M+H] ⁺ calcd 796; found, 796

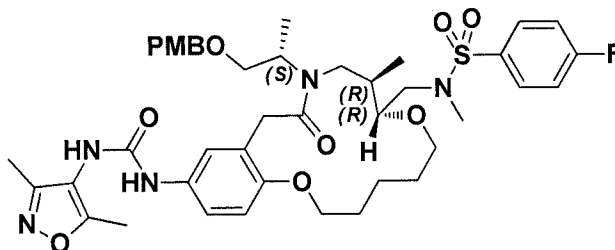
*11 was prepared from the intermediate FFF1

Alternative reduction of olefin and -NO₂ and direct conversion to urea to afford 13-16 :

5



Example 13:



10

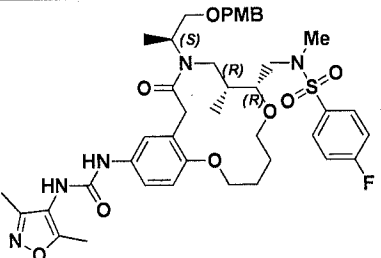
Synthesis of N-(((8R,9R)-15-(3-(3,5-dimethylisoxazol-4-yl)ureido)-11-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-9-methyl-12-oxo-3,4,5,6,8,9,10,11,12,13-decahydro-2H-benzo[h][1,10,5]dioxazacyclopentadecin-8-yl)methyl)-4-fluoro-N-methylbenzenesulfonamide

To a solution of V12 (0.040 g, 0.056 mmol) in ethylacetate (1.121 ml) was added dihydroxypalladium (3.93 mg, 5.60 μmol). The atmosphere was evacuated, and filled with a balloon of hydrogen gas. The reaction mixture was stirred for 18h. The reaction mixture was then filtered through Celite, eluting with dichloromethane. The filtrate was concentrated, and the crude material was carried on to the next step without further purification. To a solution of a portion of this crude material (0.023 g, 0.032 mmol) in THF (Volume: 0.459 ml) and AcOH (Volume: 0.459 ml) was added zinc dust (0.045 g, 0.688 mmol). The reaction was stirred for 20h. The reaction mixture was then filtered through celite, eluting with dichloromethane. The filtrate was concentrated, and the crude material was carried on to the next step without further purification. This crude material was dissolved in DCM (1.0 ml) and to this was added 3,5-dimethyl-4-isocyanato-isoxazole (9.82 μl, 0.087 mmol). The reaction mixture was stirred for 16 h. The reaction mixture was concentrated under reduced pressure and this crude material was chromatographed on silica, using methanol / dichloromethane to give the desired product (0.0065 g, 24%) as colorless resin. ¹H NMR (300 MHz, CDCl₃) δ 7.73-7.68 (m, 2H), 7.51 (s, 1H), 7.28-6.96 (m, 5H), 6.93-6.57 (m, 3H), 4.34 (dd, *J* = 25.5, 11.5, 2H), 4.04 - 3.93 (m, 2H), 3.98 - 3.71 (m, 2H), 3.69 (s, 3H), 3.47-3.36 (m, 2H), 3.30-3.01 (m, 5H), 2.67 (s, 3H), 2.53-2.44 (m, 2H), 2.24 (s, 3H), 2.11 (s, 3H), 2.00 - 1.67 (m, 3H), 1.67 - 1.28 (m, 5H), 1.26 (d, *J* = 6.8 Hz, 3H), 1.01 (d, *J* = 6.8 Hz, 3H). MS calculated for C₄₂H₅₄FN₅O₉S [M+H]⁺: 824. Found: 824.

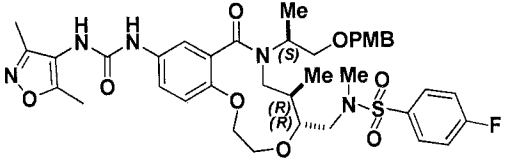
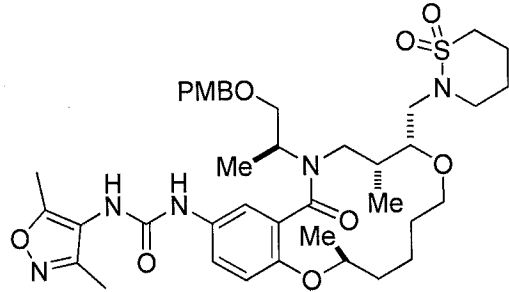
35

The following intermediate was prepared from this method starting with intermediate V13:

5

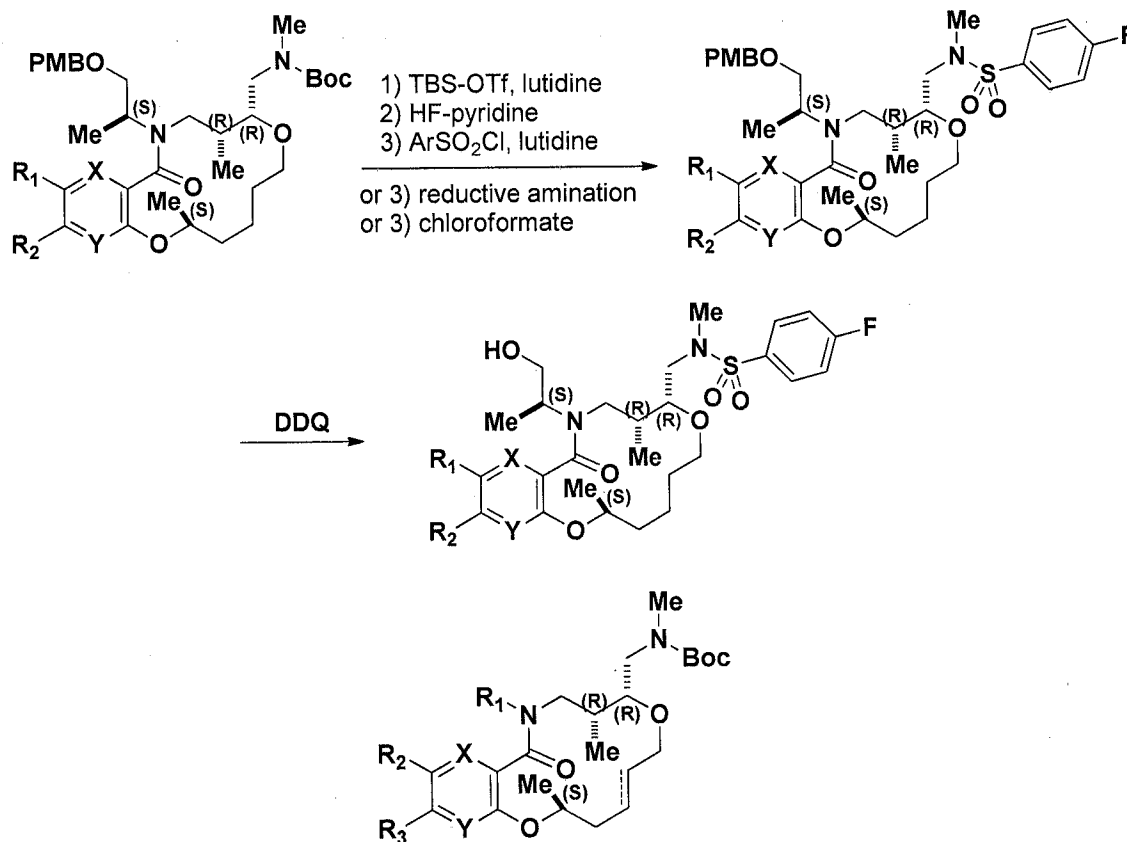
No.	Structure	Name	Mass
15A		N-(((7R,8R)-14-(3-(3,5-dimethylisoxazol-4-yl)ureido)-10-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-8-methyl-11-oxo-2,3,4,5,7,8,9,10,11,12-decahydrobenzo[h][1,10,5]dioxazacyclotetradecin-7-yl)methyl)-4-fluoro-N-methylbenzenesulfonamide	[M+H] ⁺ calcd 810; found, 810

The following examples were prepared following steps 2 and 3 from this method.

No.	Structure	Name	Mass
15B		N-(((5R,6R)-11-amino-8-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-6-methyl-9-oxo-3,5,6,7,8,9-hexahydrobenzo[e][1,4,8]dioxazacycloundecin-5-yl)methyl)-4-fluoro-N-methylbenzenesulfonamide	[M+H] ⁺ calcd 630; found, 630
16		1-(3,5-dimethylisoxazol-4-yl)-3-((2S,8R,9R)-8-((1,1-dioxido-1,2-thiazinan-2-yl)methyl)-11-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-14-yl)urea	[M+H] ⁺ calcd 770; found, 770

10

*15B was prepared from intermediate EEE2 and 16 was prepared from the intermediate AA20

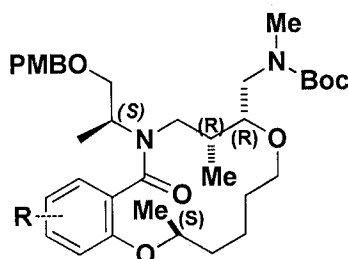
General Scheme for the synthesis of examples 18-24

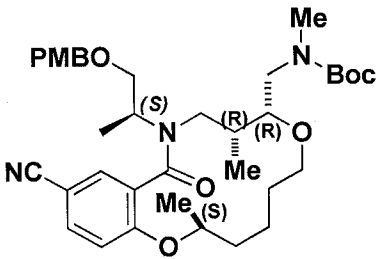
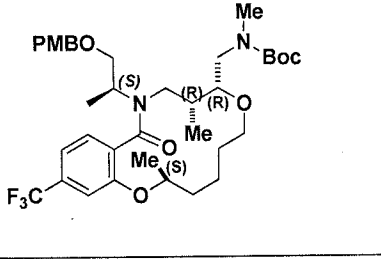
5

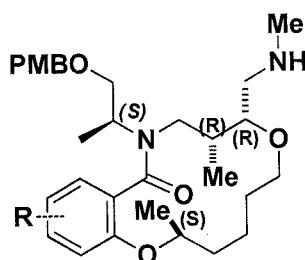
Examples 17-24 and **intermediate DD1** from steps 1 and 2 were synthesized following synthesized following the procedure previously reported in Marcaurelle, L. A.; Comer, E.; Dandapani, S.; Duvall, J. R.; Gerard, B.; Kesavan, S.; Lee, M. D, IV; Liu, H.; Lowe, J. T.; Marie, J.-C.; Mulrooney, C. A.; Pandya, B. A.; Rowley, A.; Ryba, T. D.; Suh, B.-C.; Wei, J.; Young, D. W.; Akella, L. B.; Ross, N. B.; Zhang, Y.-L.; Fass, D. M.; Reis, S. A.; Zhao, W.-N.; Haggarty, S. J.; Palmer, M.; Foley, M. A. *J. Am. Chem. Soc.* **2010**, 132, 16962-16976.

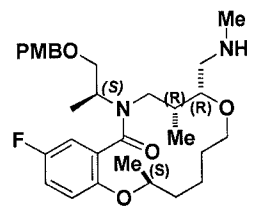
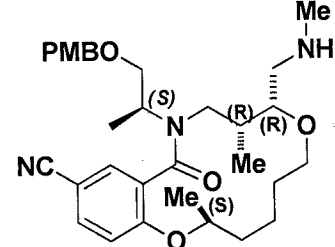
A small aliquot of select intermediates were purified via HPLC for screening examples 20-24:

15



No.	Structure	Name	MS
17		tert-butyl N-[(2S,8R,9R)-14-cyano-11-[(2S)-1-[(4-methoxyphenyl)methoxy]propan-2-yl]-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl)methyl]-N-methylcarbamate	[M+H] ⁺ calcd 638; found, 638
18		tert-butyl N-[(2S,8R,9R)-11-[(2S)-1-[(4-methoxyphenyl)methoxy]propan-2-yl]-2,9-dimethyl-12-oxo-15-(trifluoromethyl)-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl)methyl]-N-methylcarbamate	[M+H] ⁺ calcd 681; found, 681

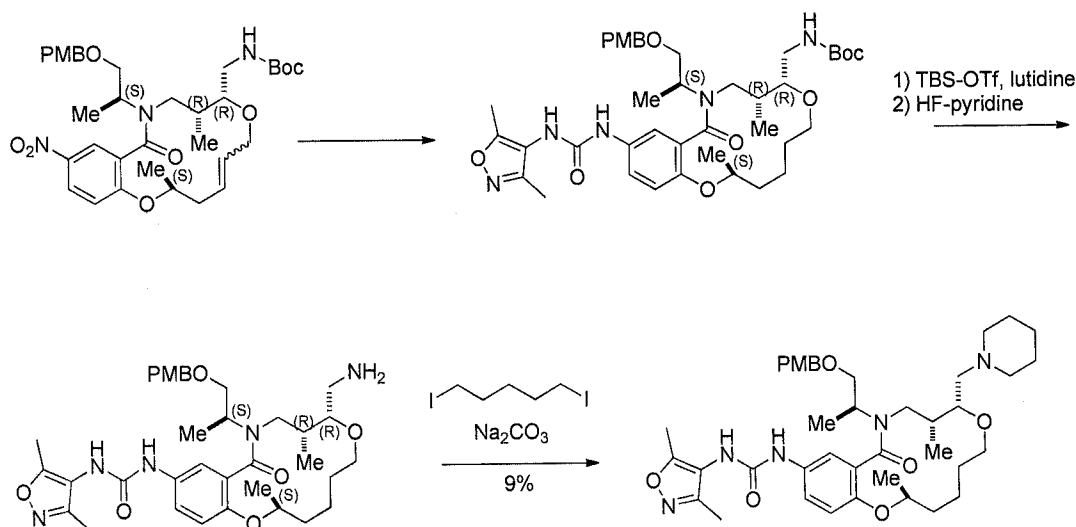
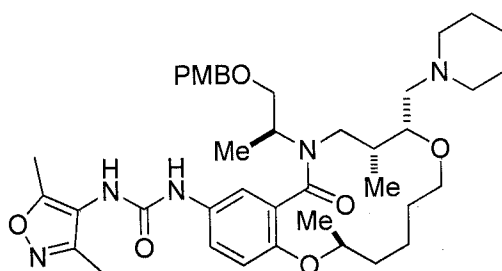


No.	Structure	Name	MS
19		(2S,8R,9R)-14-fluoro-11-[(2S)-1-[(4-methoxyphenyl)methoxy]propan-2-yl]-2,9-dimethyl-8-[(methylamino)methyl]-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-12-one	[M+H] ⁺ calcd 531.3; found, 531.3
20		(2S,8R,9R)-11-[(2S)-1-[(4-methoxyphenyl)methoxy]propan-2-yl]-2,9-dimethyl-8-[(methylamino)methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecine-14-carbonitrile	[M+H] ⁺ calcd 538.3; found, 538.3

No.	Structure	Name	MS
21		(8R,9R,15S)-6-[(2S)-1-[(4-methoxyphenyl)methoxy]propan-2-yl]-8,15-dimethyl-9-[(methylamino)methyl]-5H,6H,7H,8H,9H,11H,12H,13H,14H,15H-pyrido[2,3-b]1,9-dioxo-5-azacyclotetradecan-5-one	[M+H] ⁺ calcd 514.3; found, (MH ⁺), 514.3
22		(2S,8R,9R)-11-[(2S)-1-[(4-methoxyphenyl)methoxy]propan-2-yl]-2,9-dimethyl-8-[(methylamino)methyl]-14-(trifluoromethyl)-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-12-one	[M+H] ⁺ calcd 581.3; found, 581.3
23		1-phenyl-3-[(2S,8S,9R)-2,9,11-trimethyl-8-[(methylamino)methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]urea	[M+H] ⁺ calcd 483.3; found, 483.5
DD1		1-((2S,8R,9R)-8-(aminomethyl)-11-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-14-yl)-3-(3,5-dimethylisoxazol-4-yl)urea	[M+H] ⁺ calcd 652; found, 652

Synthesis of 24 from Intermediate V21

- 102 -

**Example 24:**

5

1-(3,5-dimethylisoxazol-4-yl)-3-((2*S*,8*R*,9*R*)-11-((*S*)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2,9-dimethyl-12-oxo-8-(piperidin-1-ylmethyl)-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[*b*][1,9,5]dioxazacyclotetradecin-14-yl)urea

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To a solution of tert-butyl (((2*S*,8*R*,9*R*)-14-(3-(3,5-dimethylisoxazol-4-yl)ureido)-11-((*S*)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[*b*][1,9,5]dioxazacyclotetradecin-8-yl)methyl)carbamate (0.027 g, 0.036 mmol) in dry CH₂Cl₂ (0.36 mL) under N₂ and chilled in an ice-H₂O bath was added 2,6-lutidine (0.017 mL, 0.15 mmol) followed by *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.022 mL, 0.091 mmol). The reaction mixture was stirred in the ice bath 30 min, then allowed to warm to rt and stirred 3 h. Additional 2,6-lutidine (0.017 mL, 0.15 mmol) was added to the mixture, then it was quenched with sat. aq. NaHCO₃. The aqueous phase was extracted into CH₂Cl₂, the organic layer dried (Na₂SO₄) and the solvent evaporated. The residue was dissolved in THF (0.5 mL) in a Teflon bottle, and HF-Pyridine (4.5 μL, 0.036 mmol) was added. The solution was stirred 45 min, then quenched with sat. aq. NaHCO₃ and the aqueous phase extracted into EtOAc. The organic layer was dried (Na₂SO₄) and the solvent evaporated. The residue (1-((2*S*,8*R*,9*R*)-8-(aminomethyl)-11-((*S*)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[*b*][1,9,5]dioxazacyclotetradecin-14-yl)-3-

15

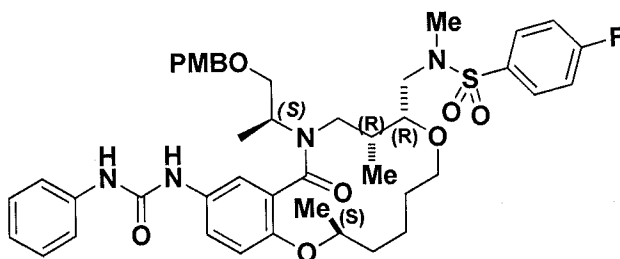
20

25

(3,5-dimethylisoxazol-4-yl)urea) was carried on to the next step without further purification.

To a solution of 1-((2*S*,8*R*,9*R*)-8-(aminomethyl)-11-((*S*)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[*b*][1,9,5]dioxazacyclotetradecin-14-yl)-3-(3,5-dimethylisoxazol-4-yl)urea (0.010 g, 0.015 mmol) in acetonitrile (0.15 mL), was added NaHCO₃ (3.9 mg, 0.046 mmol) and 1,5-diiodopentane (2.7 μ l, 0.018 mmol). The reaction mixture was stirred at rt for 16 h. Purification was accomplished by prep TLC to yield 1.0 mg (9%) of pure product. ¹H NMR (300 MHz, CDCl₃) δ 7.62-7.38 (m, 1H), 7.21 (d, *J* = 8.5 Hz, 2H), 7.18-7.08 (m, 1H), 6.88 (d, *J* = 7.8 Hz, 2H), 6.78-6.68 (m, 1H), 4.52 – 4.28 (m, 3H), 4.20 – 4.01 (m, 1H), 3.90 – 3.68 (m, 4H), 3.80 (s, 3H), 3.64 – 3.37 (m, 2H), 3.10-2.68 (m, 1H), 2.37 – 2.11 (m, 10H), 1.89-1.82 (m, 1H), 1.80-1.58 (m, 6H), 1.56-1.41 (m, 5H), 1.33 – 1.04 (m, 6H), 0.90 – 0.66 (m, 6H). MS calculated for C₄₀H₅₈N₅O₇ [M+H]⁺: 720. Found: 720.

Sulfonamide formation on Intermediates CC3-CC9, AA8, AA13-AA18, Examples 5 and 8:



4-fluoro-N-(((2*S*,8*R*,9*R*)-11-((*S*)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2,9-dimethyl-12-oxo-14-(3-phenylureido)-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[*b*][1,9,5]dioxazacyclotetradecin-8-yl)methyl)-N-methylbenzenesulfonamide (25)

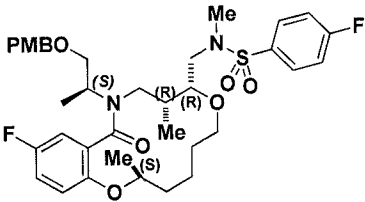
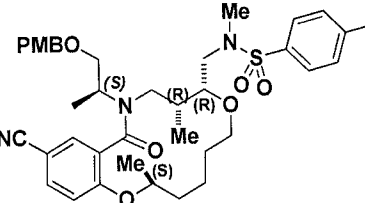
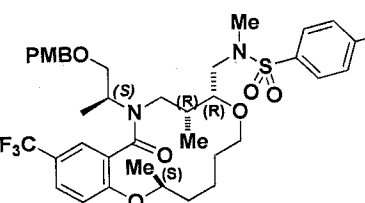
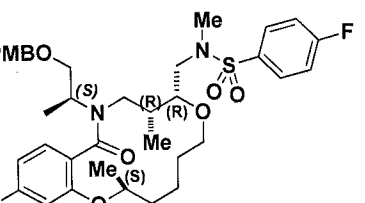
A solution of tert-butyl (((2*S*,8*R*,9*R*)-11-((*S*)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2,9-dimethyl-12-oxo-14-(3-phenylureido)-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[*b*][1,9,5]dioxazacyclotetradecin-8-yl)methyl)(methyl)carbamate (2.3 g, 3.08 mmol) in dry DCM (61.6 ml) under N₂ was chilled in a ice-H₂O bath and to this was added 2,6-dimethylpyridine (1.435 ml, 12.32 mmol) and then tert-butyldimethylsilyl trifluoromethanesulfonate (1.817 ml, 7.70 mmol) dropwise. The reaction was stirred at 0 °C for 30 min, and was then stirred at rt for a further 3h. To the solution was added 2,6-lutidine (1.4 mL) and the reaction was quenched with sat. NH₄Cl. The layers were separated, and the aqueous layer was extracted with DCM. The combined organic extracts were washed with sat. NH₄Cl and brine, dried (MgSO₄), filtered and the solvent evaporated. The residue was dissolved in THF (30 mL), transferred to a teflon bottle, then added pyridine hydrofluoride (0.382 ml, 3.08 mmol) was added. The reaction was stirred for 30 min and to this was added sat. NaHCO₃, the organic layer was dried over MgSO₄, filtered and concentrated *in vacuo* to yield the crude product which was carried onto the next step. To a solution of the residue (1.992 g, 3.08 mmol) in DCM (30.8 ml) was added 2,6-

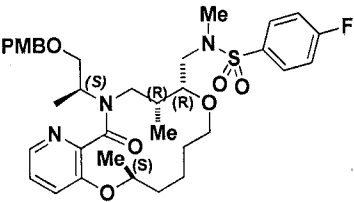
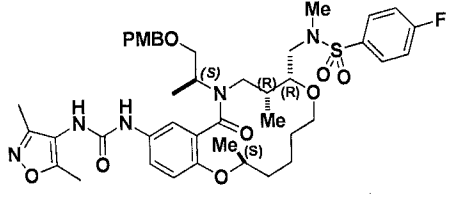
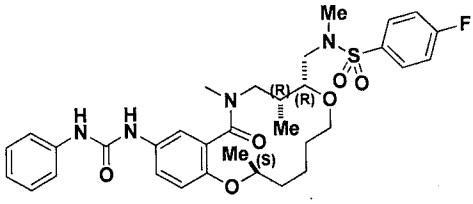
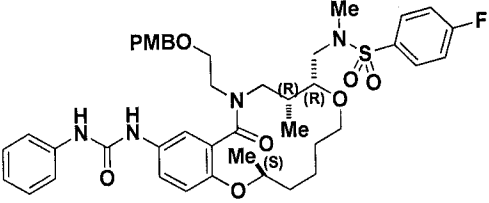
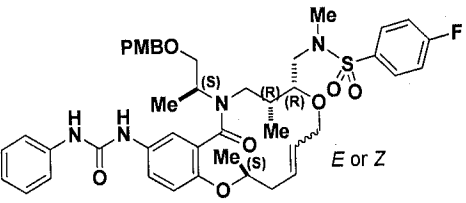
dimethylpyridine (0.717 ml, 6.16 mmol) was added 4-fluorobenzene-1-sulfonyl chloride (0.899 g, 4.62 mmol). The reaction was stirred at room temperature under N₂ overnight. To the solution was added H₂O, the layers were separated and aqueous layer extracted with DCM, washed with H₂O, dried (Na₂SO₄) and evaporated under reduced pressure. The reaction was purified by column chromatography using Ethyl acetate/hexane to afford the desired product (2.14 g, 86%). ¹HNMR (300 MHz, CDCl₃) δ 8.74–7.86 (m, 1H), 7.81–7.42 (m, 5H), 7.37–6.98 (m, 7H), 6.98–6.74 (m, 1H), 6.77–6.54 (m, 2H), 5.57–5.38 (m, 1H), 4.66–4.37 (m, 1H), 4.35–3.98 (m, 1H), 3.96–3.19 (m, 7H), 3.19–2.87 (m, 2H), 2.87–2.53 (m, 6H), 2.14–1.82 (m, 2H), 1.82–1.30 (m, 8H), 1.29–0.84 (m, 7H), 0.84–0.47 (m, 2H). MS (ESI) calcd for C₄₃H₅₃FN₄O₈S [M + H]⁺: 805. Found: 805.

The following examples were prepared using this method:

15

No.	Structure	Name	MS
26		3-[(2S,8R,9R)-11-[(2R)-1-[(4-methoxyphenyl)methoxy]propan-2-yl]-2,9-dimethyl-8-[[N-methyl(4-fluorobenzene)sulfonamido]methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecan-14-yl]-1-phenylurea	[M+H] ⁺ calcd 805; found, 805
27		4-fluoro-N-[(8R,9R,15S)-6-[(2S)-1-[(4-methoxyphenyl)methoxy]propan-2-yl]-8,15-dimethyl-5-oxo-5H,6H,7H,8H,9H,11H,12H,13H,14H,15H-pyrido[2,3-b]1,9-dioxo-5-azacyclotetradecan-9-yl]methyl]-N-methylbenzene-1-sulfonamide	[M+H] ⁺ calcd 672; found, 672

No.	Structure	Name	MS
28		4-fluoro-N-{(2S,8R,9R)-14-fluoro-11-[(2S)-1-[(4-methoxyphenyl)methoxy]propan-2-yl]-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradec-8-yl)methyl}-N-methylbenzene-1-sulfonamide	[M+H] ⁺ calcd 689; found, 689
29		N-{(2S,8R,9R)-14-cyano-11-[(2S)-1-[(4-methoxyphenyl)methoxy]propan-2-yl]-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradec-8-yl)methyl}-4-fluoro-N-methylbenzene-1-sulfonamide	[M+H] ⁺ calcd 696; found,6 96
30		4-fluoro-N-{(2S,8R,9R)-11-[(2S)-1-[(4-methoxyphenyl)methoxy]propan-2-yl]-2,9-dimethyl-12-oxo-14-(trifluoromethyl)-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradec-8-yl)methyl}-N-methylbenzene-1-sulfonamide	[M+H] ⁺ calcd 739; found,7 39
31		4-fluoro-N-{(2S,8R,9R)-11-[(2S)-1-[(4-methoxyphenyl)methoxy]propan-2-yl]-2,9-dimethyl-12-oxo-15-(trifluoromethyl)-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradec-8-yl)methyl}-N-methylbenzene-1-sulfonamide	[M+H] ⁺ calcd 739; found,7 39

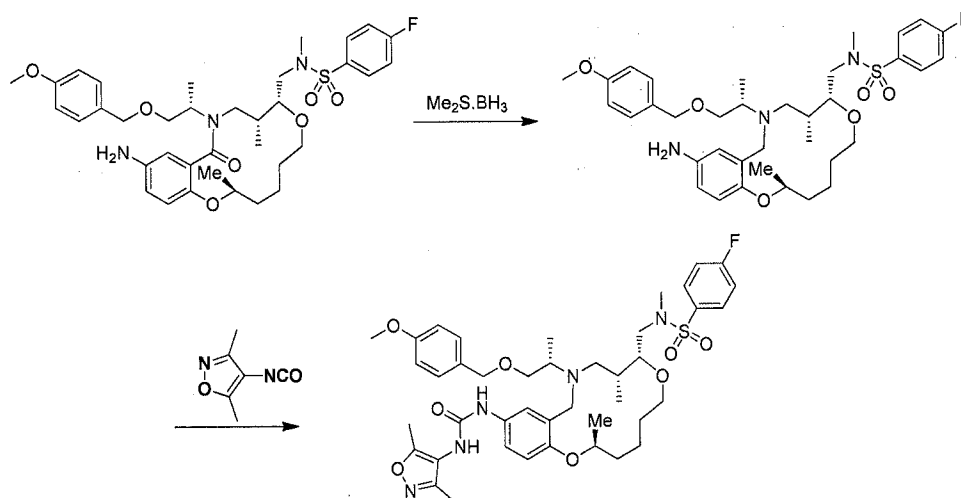
No.	Structure	Name	MS
32		4-fluoro-N-[(6S,12R,13R)-15-[(2S)-1-[(4-methoxyphenyl)methoxy]propan-2-yl]-6,13-dimethyl-16-oxo-6H,7H,8H,9H,10H,12H,13H,14H,15H,16H-pyrido[3,2-b]1,9-dioxo-5-azacyclotetradecan-12-yl)methyl]-N-methylbenzene-1-sulfonamide	[M+H] ⁺ calcd 672; found, 672
33		N-(((2S,8R,9R)-14-(3-(3,5-dimethylisoxazol-4-yl)ureido)-11-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)-4-fluoro-N-methylbenzenesulfonamide	[M+H] ⁺ calcd 824; found, 824
34		1-phenyl-3-[(2S,8S,9R)-2,9,11-trimethyl-8-[[N-methyl(4-fluorobenzene)sulfonamido]methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]urea	[M+H] ⁺ calcd 641; found, 641
35		3-[(2S,8R,9R)-11-{2-[(4-methoxyphenyl)methoxy]ethyl}-2,9-dimethyl-8-[[N-methyl(4-fluorobenzene)sulfonamido]methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	[M+H] ⁺ calcd 791; found, 791
EE1 E/Z		4-fluoro-N-(((2S,8R,9R,E/Z)-11-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2,9-dimethyl-12-oxo-14-(3-phenylureido)-2,3,6,8,9,10,11,12-octahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-	[M+H] ⁺ calcd 788; found, 788

No.	Structure	Name	MS
		yl)methyl)-N-methylbenzenesulfonamide	
EE2 E/Z		4-fluoro-N-(((2S,7R,8R,E/Z)-10-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2,8-dimethyl-11-oxo-13-(3-phenylureido)-3,7,8,9,10,11-hexahydro-2H-benzo[b][1,9,5]dioxazacyclotridecin-7-yl)methyl)-N-methylbenzenesulfonamide	[M+H] ⁺ calcd 788; found, 788
36		N-[(2S,8R,9R)-2,9-dimethyl-8-{[N-methyl(4-fluorobenzene)sulfonamido]methyl}-12-oxo-11-(propan-2-yl)-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]acetamide	[M+H] ⁺ calcd 592; found, 592
37		3-[(2S,8R,9R)-11-[(2S)-1-(tert-butoxy)propan-2-yl]-2,9-dimethyl-8-{[N-methyl(4-fluorobenzene)sulfonamido]methyl}-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	[M+H] ⁺ calcd 741; found, 741
FF		(9H-fluoren-9-yl)methyl((2S,8R,9R)-8-((4-fluoro-N-methylphenylsulfonamido)methyl)-11-isopropyl-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-14-yl)carbamate	[M+H] ⁺ calcd 772; found, 772
38		3-[(2S,8R,9R)-11-[(2S)-1-[(4-methoxyphenyl)methoxy]propan-2-yl]-2,9-dimethyl-8-[(N-methylmethanesulfonamido)methyl]-12-oxo-	[M+H] ⁺ calcd 725; found, 725

No.	Structure	Name	MS
		2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	
39		N-(((2S,8R,9R)-14-(3-(3,5-dimethylisoxazol-4-yl)ureido)-11-isopropyl-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)-4-fluoro-N-methylbenzenesulfonamide	[M+H] ⁺ calcd 688; found, 688
40		N-(((8R,9R)-14-(3-(3,5-dimethylisoxazol-4-yl)ureido)-11-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-9-methyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)-4-fluoro-N-methylbenzenesulfonamide	[M+H] ⁺ calcd 810; found, 810
41		N-(((2S,8R,9R)-14-(3-(3,5-dimethylisoxazol-4-yl)ureido)-11-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)-4-fluorobenzenesulfonamide	[M+H] ⁺ calcd 810; found, 810
42		N-(((2S,8R)-14-(3-(3,5-dimethylisoxazol-4-yl)ureido)-11-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2-methyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)-4-fluoro-N-	[M+H] ⁺ calcd 810; found, 810

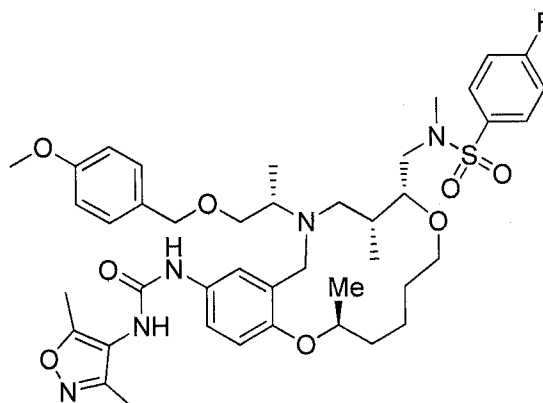
No.	Structure	Name	MS
		methylbenzenesulfonamide	

Amide Reduction and Urea Formation



5

Example 43:



10 **Synthesis of N-(((2S,8R,9R)-14-(3-(3,5-dimethylisoxazol-4-yl)ureido)-11-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2,9-dimethyl-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)-4-fluoro-N-methylbenzenesulfonamide**

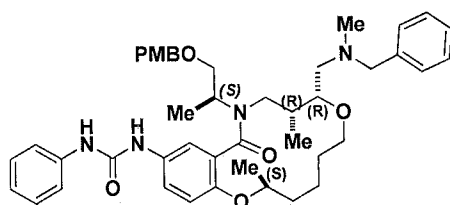
To a solution of AA7 (25mg, 0.036 mmol) in dry THF (500 μ l) under nitrogen was added dropwise over 5 min borane-methyl sulfide complex (20.74 μ l, 0.219 mmol).
 15 A reflux condenser was connected to the reaction flask and the reaction was heated to 70 $^{\circ}$ C using an oil bath. After 3h the reaction was cooled to room temperature and then MeOH was added slowly and dropwise until the bubbling slowed. More MeOH was added and the reaction was stirred at room temperature until no bubbling was seen. The solvent was removed under reduced pressure and the crude material was
 20 co-evaporated with MeOH to remove any excess of B(OMe)₃. To a solution of a portion of this crude material (13 mg, 0.019 mmol) in dry DCM (400 μ l) under nitrogen was added 4-isocyanato-3,5-dimethylisoxazole (2.61 μ l, 0.023 mmol) and

- 110 -

the reaction was stirred overnight. The reaction mixture was evaporated to dryness. This material was chromatographed on silica, using methanol / dichloromethane to give the title product (5 mg, 32%) as colorless resin. ¹H NMR (300 MHz, CDCl₃) δ 7.79-7.58 (m, 3H), 7.30-7.05 (m, 6H), 6.95-6.70 (m, 2H), 4.63-4.25 (m, 3H), 4.19-3.78 (m, 3H), 3.74-3.68 (m, 3H), 3.64-3.28 (m, 4H), 3.39-2.88 (m, 4H), 2.76-2.63 (m, 4H), 2.42 – 1.94 (m, 7H), 1.88-1.31 (m, 6H), 1.28-1.97 (m, 6H), 0.95 – 0.64 (m, 3H). MS calculated for C₄₂H₅₆FN₅O₈S [M+H]⁺: 810. Found: 810.

Reductive Amination:

10

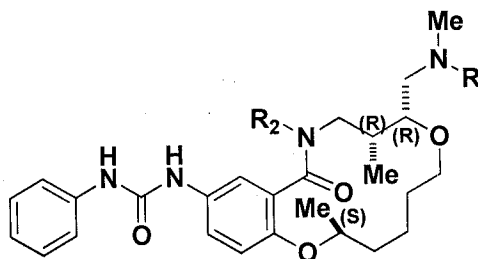


3-[(2S,8R,9R)-8-[[benzyl(methyl)amino]methyl]-11-[(2S)-1-[(4-methoxyphenyl)methoxy]propan-2-yl]-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea (44)

To a mixture of the crude amine intermediate prepared during the synthesis of Example 26 (0.078 g, 0.12 mmol) and magnesium sulfate (0.072 g, 0.600 mmol) in dry DCM (1.2 ml) was added by benzaldehyde (0.036 ml, 0.360 mmol) under N₂ atmosphere. The suspension was stirred for 1h followed by the addition of sodium triacetoxyborohydride (0.178 g, 0.840 mmol). The resulting mixture was stirred at room temperature for 4h. The reaction was diluted with DCM (10 ml) and water (10 ml). The aqueous phase was separated and washed with DCM (10 ml). Then the combined organic layers were washed with water (10 ml), separated, dried (Na₂SO₄) and evaporated to dryness. This material was chromatographed on silica, using methanol / dichloromethane to give the title product (4 mg, 5%) as colorless resin. ¹H NMR (300 MHz, CDCl₃) δ 7.72 (m, 2H), 7.53 (m, 4H), 7.37 (m, 3H), 7.23 (m, 2H), 6.84 (m, 3H), 6.63 (m, 2H), 4.47 (m, 2H), 4.33 (m, 2H), 4.22 (m, 2H), 3.78 (m, 3H), 3.36 (m, 3H), 2.73 (m, 5H), 1.59 (m, 7H), 1.23 (m, 4H), 1.03 (m, 4H), 0.90 (m, 6H), 0.59 (m, 2H). MS calculated for C₄₄H₅₆N₄O₆ [M+H]⁺: 737. Found: 737.

The following examples were prepared from this method:

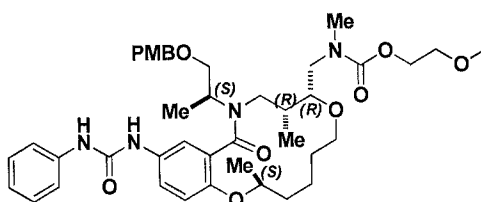
35



No.	Structure	Name	MS
45		3-[(2S,8R,9R)-8-({[(4-fluorophenyl)methyl](methyl)amino}methyl)-2,9-dimethyl-12-oxo-11-(propan-2-yl)-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradec in-14-yl]-1-phenylurea	[M+H] ⁺ calcd 619; found, 619
46		3-[(2S,8R,9R)-8-{{[(cyclohexylmethyl)(methyl)amino]methyl}-2,9-dimethyl-12-oxo-11-(propan-2-yl)-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradec in-14-yl]-1-phenylurea	[M+H] ⁺ calcd 607; found, 607
47		3-[(2S,8R,9R)-8-{{[benzyl(methyl)amino]methyl}-2,9-dimethyl-12-oxo-11-(propan-2-yl)-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradec in-14-yl]-1-phenylurea	[M+H] ⁺ calcd 601; found, 601
48		3-[(2S,8R,9R)-8-({[(4-methoxyphenyl)methyl](methyl)amino}methyl)-2,9-dimethyl-12-oxo-11-(propan-2-yl)-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradec in-14-yl]-1-phenylurea	[M+H] ⁺ calcd 631; found, 631
49		3-[(2S,8R,9R)-8-{{[(cyclohexylmethyl)(methyl)amino]methyl}-11-[(2S)-1-(4-methoxyphenyl)methoxy]propan-2-yl]-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradec in-14-yl]-1-phenylurea	[M+H] ⁺ calcd 743; found, 743

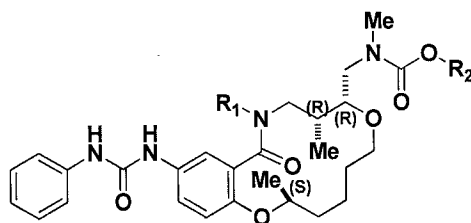
No.	Structure	Name	MS
50		1-((2S,8R,9R)-8-(((4-methoxybenzyl)(methyl)amino)methyl)-11-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-14-yl)-3-phenylurea	[M+H] ⁺ calcd 767; found, 767

Synthesis of carbamates:



- 5 **2-methoxyethyl (((2S,8R,9R)-11-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2,9-dimethyl-12-oxo-14-(3-phenylureido)-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)(methyl)carbamate (GG)**
- 10 To a solution of crude amine intermediate prepared during the synthesis of Example 26 (0.22, 0.340 mmol) in dioxane (8.50 ml) under N₂ was added a 10% Sodium Bicarbonate (1.648 ml, 2.041 mmol) aqueous solution, followed by 2-methoxyethyl chloroformate (0.079 ml, 0.680 mmol). The reaction mixture was stirred at room temperature for 15h. The reaction was diluted with EtOAc and water. The aqueous
- 15 phase was separated and washed with EtOAc, then the combined organic layers were washed with water and brine, dried over Na₂SO₄ and evaporated to dryness. This material was chromatographed on silica, using methanol / dichloromethane to give 0.15 g (59%) of the final product as colorless resin. ¹H NMR (300 MHz, CDCl₃)
- 20 δ 7.60 (m, 2H), 7.41 (m, 2H), 7.37 – 7.12 (m, 3H), 6.97 (m, 1H), 6.93 – 6.81 (m, 2H), 6.75 (m, 2H), 5.31 (s, 1H), 4.50 (m, 2H), 4.34 (m, 1H), 4.19 (m, 2H), 3.97 (m, 2H), 3.79 (m, 3H), 3.74 – 3.44 (m, 4H), 3.44 – 3.25 (m, 3H), 3.22 (m, 1H), 3.00 (m, 4H), 2.78 – 2.58 (m, 1H), 2.11 (m, 2H), 1.52 (m, 9H), 1.23 (m, 6H), 1.08 (m, 2H), 0.81 (m, 1H). MS calculated for C₄₁H₅₆N₄O₉ : 749 [M+H]⁺. Found 749.
- 25 The following intermediate **HH** and example **52** were prepared from this method:

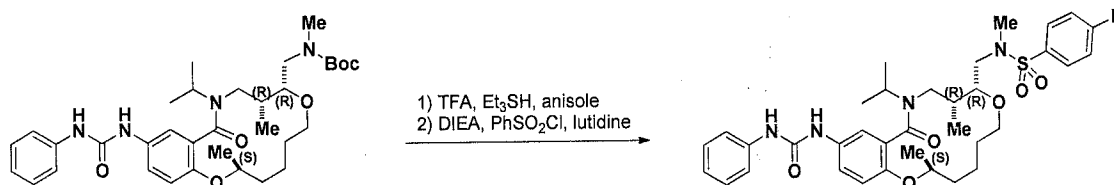
- 113 -



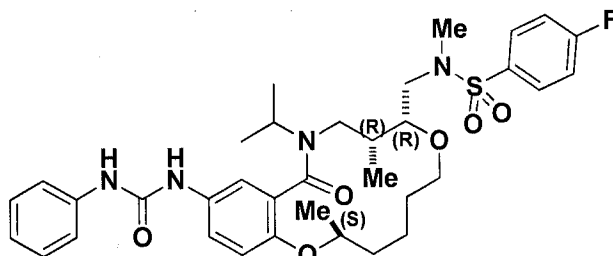
No.	Structure	Name	MS
HH		phenyl (((2S,8R,9R)-11-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2,9-dimethyl-12-oxo-14-(3-phenylureido)-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)(methyl)carbamate	[M+H] ⁺ calcd 766; found, 766
51		(2S)-2-[(2S,8R,9R)-8-({[(tert-butoxy)carbonyl](methyl)amino}methyl)-2,9-dimethyl-12-oxo-14-[(phenylcarbamoyl)amino]-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-11-yl)propyl benzoate	[M+H] ⁺ calcd 731.4; found, 731.5

Alternative Boc-deprotection and sulfonylation:

5

10 Example 52:

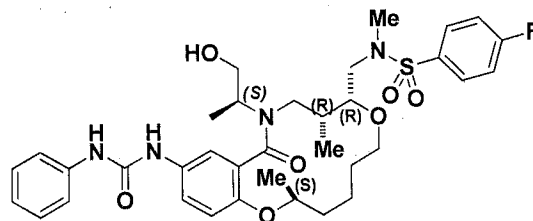
- 114 -



3-[(2S,8R,9R)-2,9-dimethyl-8-{[N-methyl(4-fluorobenzene)sulfonamido]methyl}-12-oxo-11-(propan-2-yl)-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea (52)

To a solution of Boc-protected amine **CC2** (0.0615 g, 0.101 mmol) in dry DCM (2.014 ml) was added anisole (0.109 ml, 1.007 mmol), triethylsilane (0.016 ml, 0.101 mmol), and 2,2,2-trifluoroacetic acid (0.187 ml, 2.52 mmol) under N₂ atmosphere. The resulting mixture was stirred at room temperature for 90 min. The solution was then evaporated and azeotroped with toluene (3 X) and finally dried under high vacuum. The crude amine (0.0727 g, 0.142 mmol) was re-dissolved in DCM (1.424 ml), then N-ethyl-N-isopropylpropan-2-amine (0.025 ml, 0.142 mmol) was added, followed by 2,6-dimethylpyridine (0.099 ml, 0.854 mmol), and 4-fluorobenzene-1-sulfonyl chloride (0.055 g, 0.285 mmol). The resulting mixture was stirred at room temperature for 15h. The reaction was diluted with DCM (10 ml) and washed with water (2 X 10 ml). The organic phase was then separated, dried (Na₂SO₄) and evaporated to dryness. This material was chromatographed on silica, using methanol / dichloromethane to give the final product (39 mg, 41% over 2 steps) as colorless resin. ¹H NMR (300 MHz, CDCl₃) δ 7.81 – 7.65 (m, 2H), 7.53 – 7.29 (m, 1H), 7.39 – 7.29 (m, 1H), 7.27 – 7.19 (m, 1H), 7.17 – 7.10 (m, 2H), 7.07 – 7.01 (m, 1H), 6.88 – 6.92 (m, 2H), 6.89 – 6.84 (m, 1H), 6.81 – 6.74 (m, 1H), 4.48 (s, 1H), 4.01 – 3.68 (m, 3H), 3.62 – 3.40 (m, 1H), 3.13 – 2.95 (m, 1H), 2.92 – 2.80 (m, 2H), 2.79 – 2.71 (m, 1H), 2.69 – 2.57 (m, 1H), 2.54 – 2.42 (m, 4H), 2.39 – 2.14 (m, 1H), 1.88 – 1.67 (m, 1H), 1.65 – 1.58 (m, 8H), 1.52 – 1.38 (m, 2H), 1.33 – 1.18 (m, 2H), 1.14 – 1.06 (m, 1H), 1.04 – 0.88 (m, 3H), 0.85 – 0.73 (d, 1H). MS calculated for C₃₅H₄₅FN₄O₆S [M+H]⁺: 669. Found: 669.

Deprotection of the –PMB ether:

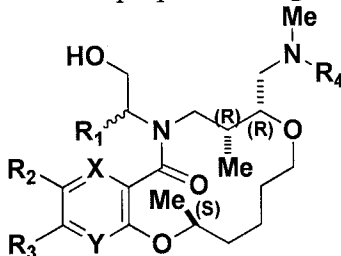


4-fluoro-N-(((2S,8R,9R)-11-((S)-1-hydroxypropan-2-yl)-2,9-dimethyl-12-oxo-14-(3-phenylureido)-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl))-N-methyl-4-fluorobenzene sulfonamide

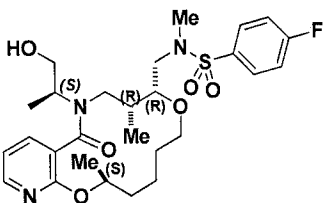
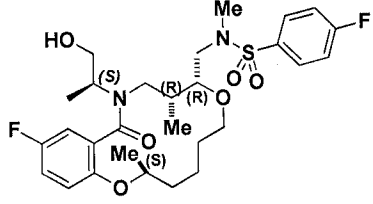
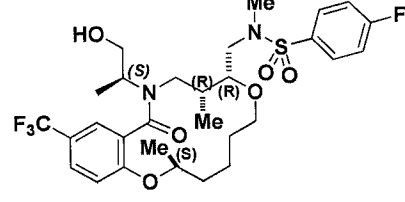
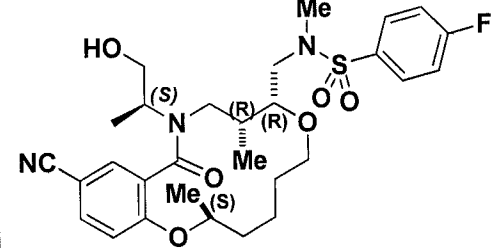
decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)-N-methylbenzenesulfonamide (53)

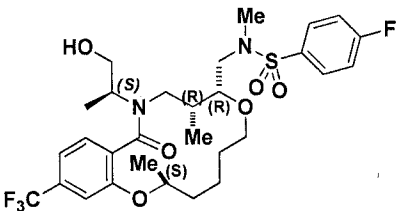
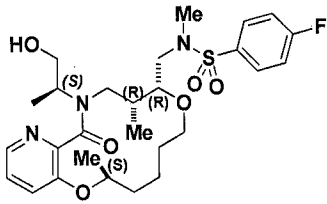
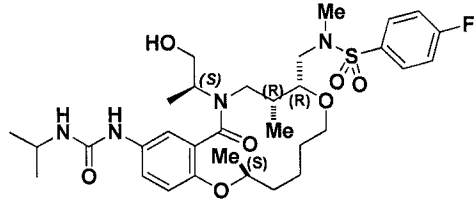
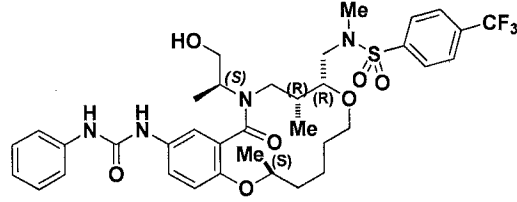
To a solution of 4-fluoro-N-(((2S,8R,9R)-11-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2,9-dimethyl-12-oxo-14-(3-phenylureido)-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)-N-methylbenzenesulfonamide (1.99 g, 2.472 mmol) in DCM (24.72 ml) was added 2.5 mL pH 7 buffer. The reaction mixture was cooled to 0 °C in an ice-H₂O bath. To this mixture was added 4,5-dichloro-3,6-dioxocyclohexa-1,4-diene-1,2-dicarbonitrile (0.730 g, 3.21 mmol) and the mixture was stirred under N₂ for 16h, allowing warming to rt. The reaction was quenched with sat. NaHCO₃, and stirred for 1 h. The phases were separated and the aqueous phase was washed with DCM twice. The organic phases were combined and washed with saturated NaHCO₃ and H₂O. The organic components were dried (Na₂SO₄) and evaporated under reduced pressure to afford crude material. The reaction was purified by column chromatography using Ethylacetate/hexane to afford the desired product (1.41 g, 83%). ¹HNMR (300 MHz, CDCl₃) δ 8.17–7.49 (m, 3H), 7.46–7.08 (m, 7H), 7.07–6.59 (m, 2H), 4.73–4.53 (m, 1H), 4.51–4.22 (m, 1H), 4.11–3.62 (m, 3H), 3.62–3.24 (m, 4H), 3.24–2.93 (m, 4H), 2.93–2.59 (m, 5H), 2.45–1.94 (m, 2H), 1.84–1.25 (m, 5H), 1.22–0.92 (m, 6H), 0.91–0.65 (m, 2H). MS (ESI) calcd for C₃₅H₄₅FN₄O₇S [M + H]⁺: 685. Found: 685.

The following examples were prepared using this method:

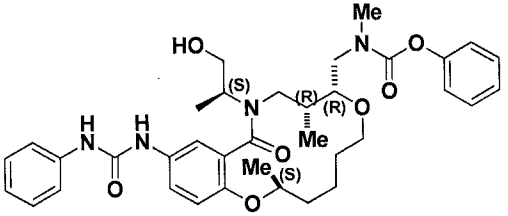
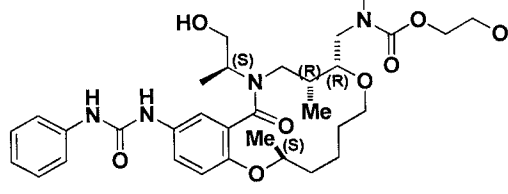
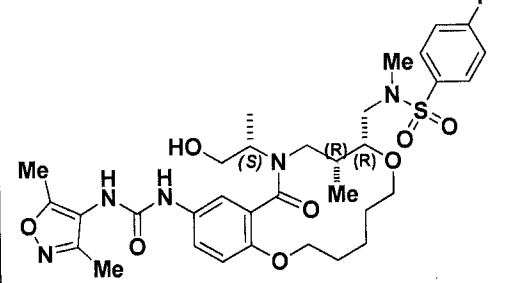
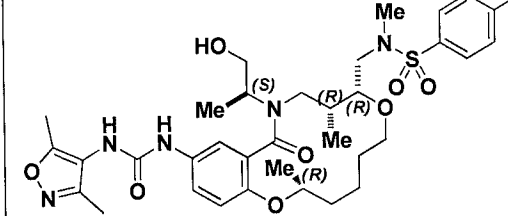


No.	Structure	Name	MS
54		3-[(2S,8R,9R)-11-[(2R)-1-hydroxypropan-2-yl]-2,9-dimethyl-8-[[N-methyl(4-fluorobenzene)sulfonamido]methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	[M+H] ⁺ calcd 685; found, 685

No.	Structure	Name	MS
55		4-fluoro-N- {[(8R,9R,15S)-6- [(2S)-1- hydroxypropan-2- yl]-8,15-dimethyl-5- oxo- 5H,6H,7H,8H,9H,11 H,12H,13H,14H,15H- pyrido[2,3-b]1,9- dioxo-5- azacyclotetradecan- 9-yl]methyl}-N- methylbenzene-1- sulfonamide	[M+H] ⁺ calcd 552; found, 552
56		4-fluoro-N- {[(2S,8R,9R)-14- fluoro-11-[(2S)-1- hydroxypropan-2- yl]-2,9-dimethyl-12- oxo- 2,3,4,5,6,8,9,10,11,12- decahydro-1,7,11- benzodioxazacyclotet radecin-8-yl]methyl}- N-methylbenzene-1- sulfonamide	[M+H] ⁺ calcd 569; found, 569
57		4-fluoro-N- {[(2S,8R,9R)-11- [(2S)-1- hydroxypropan-2- yl]-2,9-dimethyl-12- oxo-14- (trifluoromethyl)- 2,3,4,5,6,8,9,10,11,12- decahydro-1,7,11- benzodioxazacyclotet radecin-8-yl]methyl}- N-methylbenzene-1- sulfonamide	[M+H] ⁺ calcd 619; found, 619
58		N-[(2S,8R,9R)-14- cyano-11-[(2S)-1- hydroxypropan-2- yl]-2,9-dimethyl-12- oxo- 2,3,4,5,6,8,9,10,11,12- decahydro-1,7,11- benzodioxazacyclotet radecin-8-yl]methyl}- 4-fluoro-N-	[M+H] ⁺ calcd 576; found, 576

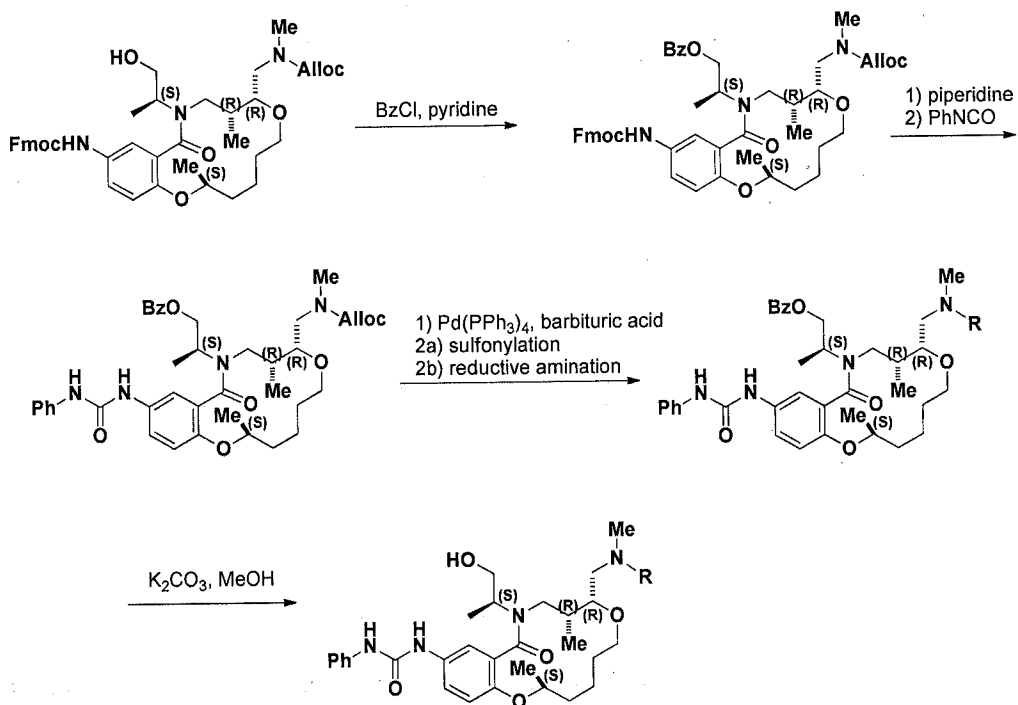
No.	Structure	Name	MS
		methylbenzene-1-sulfonamide	
59		4-fluoro-N- {[(2S,8R,9R)-11- [(2S)-1- hydroxypropan-2- yl]-2,9-dimethyl-12- oxo-15- (trifluoromethyl)- 2,3,4,5,6,8,9,10,11,12- decahydro-1,7,11- benzodioxazacyclotet radecin-8-yl]methyl}- N-methylbenzene-1- sulfonamide	[M+H] ⁺ calcd 619; found, 619
60		4-fluoro-N- {[(6S,12R,13R)-15- [(2S)-1- hydroxypropan-2- yl]-6,13-dimethyl-16- oxo- 6H,7H,8H,9H,10H,12 H,13H,14H,15H,16H- pyrido[3,2-b]1,9- dioxazacyclotetradecan- 12-yl]methyl}-N- methylbenzene-1- sulfonamide	[M+H] ⁺ calcd 552; found, 552
61		1-[(2S,8R,9R)-11- [(2S)-1- hydroxypropan-2- yl]-2,9-dimethyl-8- {[N-methyl(4- fluorobenzene)sulfon amido]methyl}-12- oxo- 2,3,4,5,6,8,9,10,11,12- decahydro-1,7,11- benzodioxazacyclotet radecin-14-yl]-3- (propan-2-yl)urea	[M+H] ⁺ calcd 651; found, 651
62		3-[(2S,8R,9R)-11- [(2S)-1- hydroxypropan-2- yl]-2,9-dimethyl-8- ([N-methyl[4- (trifluoromethyl)ben zene]sulfonamido)me	[M+H] ⁺ calcd 735; found, 735

No.	Structure	Name	MS
		thyl)-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	
63		3-[(2S,8R,9R)-11-(2-hydroxyethyl)-2,9-dimethyl-8-[[N-methyl(4-fluorobenzene)sulfonamido]methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	[M+H] ⁺ calcd 671; found, 671
64 E/Z		3-[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-8-[[N-methyl(4-fluorobenzene)sulfonamido]methyl]-12-oxo-2,3,6,8,9,10,11,12-octahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	[M+H] ⁺ calcd 683; found, 683
65 E/Z		3-[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-8-[[N-methyl(4-fluorobenzene)sulfonamido]methyl]-12-oxo-2,3,6,8,9,10,11,12-octahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	[M+H] ⁺ calcd 683; found, 683

No.	Structure	Name	MS
66		phenyl N- {[(2S,8R,9R)-11- [(2S)-1- hydroxypropan-2- yl]-2,9-dimethyl-12- oxo-14- [(phenylcarbamoyl)a mino]- 2,3,4,5,6,8,9,10,11,12- decahydro-1,7,11- benzodioxazacyclotet radecin-8-yl)methyl]}- N-methylcarbamate	[M+H]⁺ calcd 647; found, 647
67		2-methoxyethyl N- {[(2S,8R,9R)-11- [(2S)-1- hydroxypropan-2- yl]-2,9-dimethyl-12- oxo-14- [(phenylcarbamoyl)a mino]- 2,3,4,5,6,8,9,10,11,12- decahydro-1,7,11- benzodioxazacyclotet radecin-8-yl)methyl]}- N-methylcarbamate	[M+H]⁺ calcd 629; found, 629
68		N-(((8R,9R)-14-(3- (3,5- dimethylisoxazol-4- yl)ureido)-11-((S)-1- hydroxypropan-2- yl)-9-methyl-12-oxo- 2,3,4,5,6,8,9,10,11,12- decahydrobenzo[b][1 ,9,5]dioxazacyclotet radecin-8-yl)methyl)- 4-fluoro-N- methylbenzenesulfon amide	[M+H]⁺ calcd 690; found,6 90
69		N-(((2R,8R,9R)-14- (3-(3,5- dimethylisoxazol-4- yl)ureido)-11-((S)-1- hydroxypropan-2- yl)-2,9-dimethyl-12- oxo- 2,3,4,5,6,8,9,10,11,12- decahydrobenzo[b][1 ,9,5]dioxazacyclotet	[M+H]⁺ calcd 704; found 704,

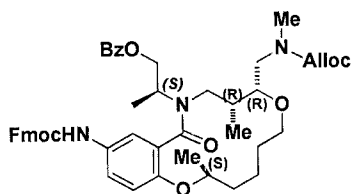
No.	Structure	Name	MS
		radecin-8-yl)methyl)-4-fluoro-N-methylbenzenesulfonamide	
70		4-fluoro-N-(((8R,9R)-11-((S)-1-hydroxypropan-2-yl)-9-methyl-14-nitro-12-oxo-2,3,6,8,9,10,11,12-octahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)-N-methylbenzenesulfonamide	[M+H] ⁺ calcd 580; found 580,

Alternate synthesis of intermediates II-JJ and examples 71-72 :



5

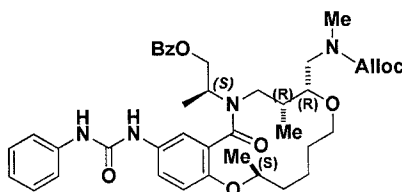
Intermediate II:



(S)-2-((2S,8R,9R)-14-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)-8-(((allyloxy)carbonyl)(methyl)amino)methyl)-2,9-dimethyl-12-oxo-3,4,5,6,9,10-hexahydrobenzo[b][1,9,5]dioxazacyclotetradecin-11(2H,8H,12H)-yl)propyl benzoate (II)

To a solution of allyl (((2S,8R,9R)-14-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)-11-((S)-1-hydroxypropan-2-yl)-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)(methyl)carbamate (0.509 g, 0.713 mmol) in dry DCM (5.94 ml) was added pyridine (0.577 ml, 7.13 mmol) followed by benzoyl chloride (0.248 ml, 2.139 mmol) under N₂ atmosphere at room temperature. The resulting mixture was stirred at room temperature for 4h. The reaction was diluted with DCM (10 ml) and washed with water (2 X 10 ml). The organic phase was then separated, dried (Na₂SO₄) and evaporated to dryness. This material was chromatographed on silica, using ethyl acetate / hexanes to give 0.54 g (93%) of the desired product. ¹H NMR (300 MHz, CDCl₃) δ 8.05 (d, 1H), 8.00 (d, 1H), 7.77 (d, 2H), 7.66-7.50 (m, 3H), 7.48 – 7.37 (m, 4H), 7.36-7.28 (m, 2H), 7.22-7.11 (m, 1H), 6.89-6.66 (m, 2H), 6.03-5.78 (m, 1H), 5.26 – 5.06 (m, 1H), 4.72-4.40 (m, 4H), 4.32-4.22 (m, 1H), 4.18 – 4.02 (m, 1H), 4.00-3.84 (m, 1H), 3.80-3.50 (m, 1H), 3.47 (d, 2H), 3.41 – 3.15 (m, 1H), 3.12-2.73 (m, 3H), 2.19 (m, 1H), 2.04 (m, 1H), 1.91-1.69 (m, 2H), 1.67-1.45 (m, 3H), 1.37-1.08 (m, 9H), 0.99-0.80 (m, 6H), 0.77 (m, 2H). MS calculated for C₄₈H₅₅N₃O₉ [M+H]⁺: 818. Found: 818.

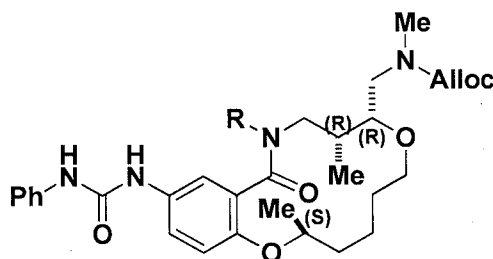
Intermediate JJ:



A mixture of Fmoc-protected aniline (1.61 g, 1.968 mmol) and piperidine (0.390 ml, 3.94 mmol) in dry DMF (19.68 ml) was stirred under N₂ atmosphere at room temperature for 40 min. Then phenyl isocyanate (0.209 ml, 1.914 mmol) was introduced to the reaction mixture, which was stirred at room temperature for 3 h. The reaction was diluted with water/EtOAc (10 ml) and extracted with EtOAc. The organic phase was separated, washed with water, brine, dried (Na₂SO₄) and evaporated to dryness. This material was chromatographed on silica, using ethyl acetate / hexanes to afford the desired product (0.77 g, 60% over 2 steps). ¹H NMR (300 MHz, CDCl₃) δ 8.06 (m, 1H), 8.04 – 7.89 (m, 1H), 7.81 (m, 1H), 7.59 (m, 2H), 7.51 – 7.30 (m, 2H), 7.23 (m, 2H), 6.96 (m, 1H), 6.82 (m, 1H), 6.69 (m, 1H), 5.89 (m, 1H), 5.45 – 5.08 (m, 2H), 4.83 (m, 1H), 4.55 (m, 3H), 4.18 – 4.02 (m, 1H), 3.93 (m, 2H), 3.50 (m, 1H), 3.34 (m, 1H), 3.26 – 2.95 (m, 3H), 2.88 (m, 3H), 2.26 (m, 1H), 2.04 (m, 1H), 1.77 (m, 2H), 1.62 (m, 2H), 1.38 (m, 3H), 1.24 (m, 5H), 1.14 – 1.00 (m, 2H), 0.99 – 0.85 (m, 2H), 0.77 (m, 2H). MS calculated for C₄₀H₅₀N₄O₈ [M+H]⁺: 715. Found: 715.

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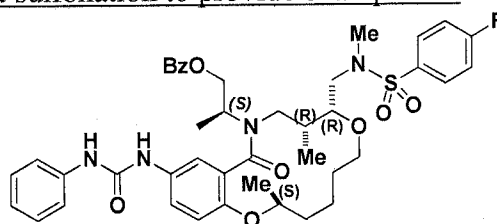
The following example was prepared from this method:



No.	Structure	Name	MS
71		(R)-2-((2S,8R,9R)-8-(((allyloxy)carbonyl)(methyl)amino)methyl)-2,9-dimethyl-12-oxo-14-(3-phenylureido)-3,4,5,6,9,10-hexahydrobenzo[b][1,9,5]dioxazacyclotetradecin-11(2H,8H,12H)-yl)propyl benzoate	[M+H] ⁺ calcd 715; found, 715

5

Alloc deprotection and sulfonation to provide example 72:

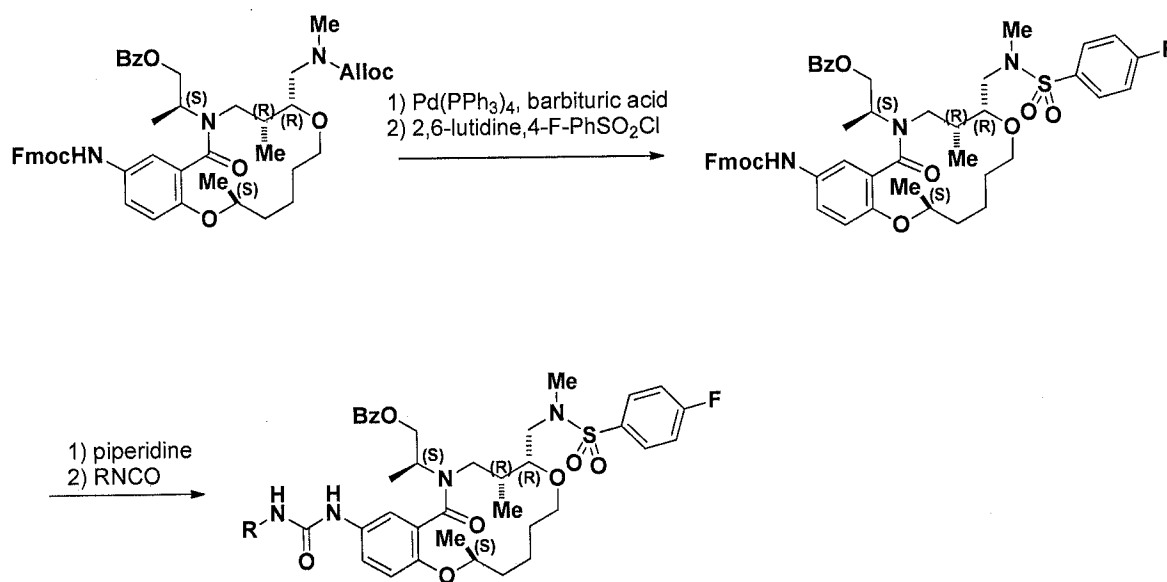


- 10 **(2S)-2-[(2S,8R,9R)-2,9-dimethyl-8-{[N-methyl(4-fluorobenzene)sulfonamido]methyl}-12-oxo-14-[(phenylcarbamoyl)amino]-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-11-yl]propyl benzoate (72)**
- 15 A mixture of Alloc-protected amine (0.77 g, 1.077 mmol), 1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (1.261 g, 8.08 mmol) and Pd (PPh₃)₄ (0.249 g, 0.215 mmol) in dry DCM (15.39 ml) was stirred under N₂ atmosphere at room temperature for 1 h. The reaction mixture was diluted with DCM (25 ml), washed with Sat. NaHCO₃ (2 X 25 ml) and water (2 X 25 ml). The organic phase was separated, dried
- 20 (Na₂SO₄) and evaporated to dryness. The crude product was then re-dissolved in dry DCM (10.77 ml), then 2,6-lutidine (0.878 ml, 7.54 mmol) was added, followed by 4-fluorobenzene-1-sulfonyl chloride (0.419 g, 2.154 mmol) under N₂ atmosphere. The resulting mixture was stirred at room temperature for 15h. The reaction was diluted with DCM (25 ml) and washed with water (2 X 25 ml). The organic layer was
- 25 separated, dried (Na₂SO₄) and evaporated to dryness. This material was chromatographed on silica, using ethyl acetate / hexanes to give 0.53 g (62%) of the title product as colorless resin. ¹H NMR (300 MHz, CDCl₃) δ 8.11 – 7.84 (m, 2H),

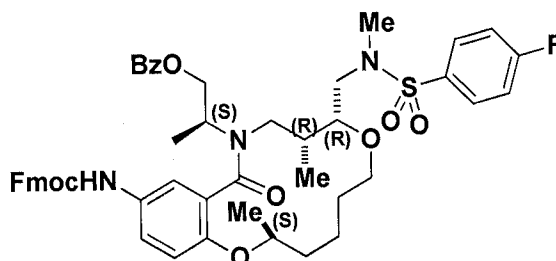
- 123 -

7.79 (m, 1H), 7.62 (m, 3H), 7.37 (m, 2H), 7.34 – 7.16 (m, 2H), 7.04 (m, 4H), 6.87 – 6.63 (m, 2H), 6.52 (m, 1H), 4.89 – 4.48 (m, 1H), 4.45 – 4.18 (m, 1H), 4.06 (m, 1H), 3.77 (m, 2H), 3.50 (m, 1H), 3.35 (m, 1H), 2.94 (m, 2H), 2.64 (m, 5H), 1.88 (m, 1H), 1.56 (m, 2H), 1.43 (m, 2H), 1.31 (m, 4H), 1.04 (m, 3H), 0.88 (m, 2H), 0.75 (m, 1H), 0.60 (m, 2H), 0.37 (m, 1H). MS calculated for $C_{42}H_{49}FN_4O_8S$ $[M+H]^+$: 789. Found: 789.

Alternate synthetic order to prepare Intermediates KK-MM:



Intermediate **KK**:

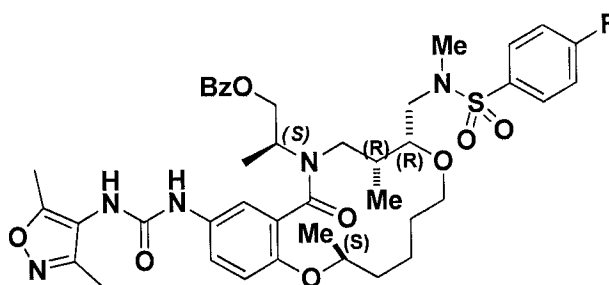


(S)-2-((2S,8R,9R)-14-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)-8-((4-fluoro-N-methylphenylsulfonamido)methyl)-2,9-dimethyl-12-oxo-3,4,5,6,9,10-hexahydrobenzo[b][1,9,5]dioxazacyclotetradecin-11(2H,8H,12H)-yl)propyl benzoate (KK)

A mixture of Alloc-protected amine **II** (0.268 g, 0.328 mmol), 1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (0.384 g, 2.46 mmol) and $Pd(PPh_3)_4$ (76 mg, 0.066 mmol) in dry CH_2Cl_2 (4.7 ml) was stirred under N_2 atmosphere at room temperature for 1 h. The reaction mixture was diluted with CH_2Cl_2 , washed with Sat. $NaHCO_3$ and water, dried (Na_2SO_4) and evaporated to dryness. The crude product was then re-dissolved in dry CH_2Cl_2 (3.3 ml), then 2,6-lutidine (0.27 ml, 2.3

- 124 -

mmol) was added, followed by 4-fluorobenzene-1-sulfonyl chloride (0.127 g, 0.654 mmol) under N₂ atmosphere. The resulting mixture was stirred at room temperature for 15 h. The reaction was diluted with CH₂Cl₂ and washed with water, dried (Na₂SO₄) and evaporated to dryness. This material was chromatographed on silica, using ethyl acetate / hexanes to give 0.20 g (70%) of the title product as colorless resin. ¹H NMR (300 MHz, CDCl₃) δ 8.08-7.95 (m, 2H), 7.86 – 7.67 (m, 4H), 7.65-7.49 (m, 3H), 7.48-7.37 (m, 4H), 7.36 – 7.23 (m, 3H), 7.22-7.09 (m, 3H), 6.88 – 6.74 (m, 1H), 6.68 (m, 1H), 4.89 – 4.58 (m, 1H), 4.57 – 4.40 (m, 3H), 4.30-4.17 (m, 1H), 4.06 (m, 1H), 3.99-3.80 (m, 2H), 3.78-3.40 (m, 2H), 3.20-2.87 (m, 2H), 2.86-2.68 (m, 3H), 2.28-2.15 (m, 1H), 2.07-1.89 (m, 1H), 1.86-1.52 (m, 4H), 1.52-1.29 (m, 6H), 1.23-1.08 (m, 3H), 1.01-0.70 (m, 3H). MS calculated for C₅₀H₅₄FN₃O₉S [M+H]⁺: 892. Found: 892.



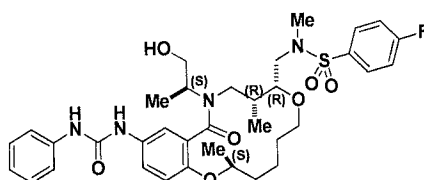
(S)-2-((2S,8R,9R)-14-(3-(3,5-dimethylisoxazol-4-yl)ureido)-8-((4-fluoro-N-methylphenylsulfonamido)methyl)-2,9-dimethyl-12-oxo-3,4,5,6,9,10-hexahydrobenzo[b][1,9,5]dioxazacyclotetradecin-11(2H,8H,12H)-yl)propyl benzoate (LL)

To a solution of Fmoc protectec aniline (60 mg, 0.067 mmol) in dry DMF (0.67 ml) was added piperidine (0.013 mL, 0.14 mmol). The reaction mixture was stirred for 1h, then 4-isocyanato-3,5-dimethylisoxazole (0.030 mL, 0.27 mmol) was added and the mixture stirred for 2 h. The mixture was then diluted with EtOAc and H₂O, separated phases and washed aq. with EtOAc. The combined organics were washed with H₂O, dried (Na₂SO₄) and the solvent evaporated. This material was chromatographed on silica, using MeOH / DCM to yield 22 mg (41%) of product. ¹H NMR (300 MHz, CDCl₃) δ 8.12-7.92 (m, 2H), 7.91 – 7.62 (m, 3H), 7.61-7.49 (m, 1H), 7.48-7.33 (m, 2H), 7.22 – 7.08 (m, 2H), 7.05-6.69 (m, 3H), 4.98-4.30 (m, 3H), 4.25-4.02 (m, 1H), 3.98 – 3.79 (m, 1H), 3.77-3.60 (m, 1H), 3.57-3.27 (m, 1H), 3.23 – 2.95 (m, 2H), 2.94-2.68 (m, 3H), 2.36-2.00 (m, 6H), 1.85-1.70 (m, 2H), 1.63-1.33 (m, 5H), 1 (m, 2H), 1.32– 1.02 (m, 6H), 1.05-0.77 (m, 3H). MS calculated for C₄₁H₅₀FN₅O₉S [M+H]⁺: 808. Found: 808.

The following intermediate **MM** was prepared from this method:

No.	Structure	Name	MS
M M		(S)-2-((2S,8R,9R)-14-(benzo[d]oxazol-2-ylamino)-8-((4-fluoro-N-methylphenylsulfonamido)methyl)-2,9-dimethyl-12-oxo-3,4,5,6,9,10-hexahydrobenzo[b][1,9,5]dioxazacyclotetradecin-11(2H,8H,12H)-yl)propyl benzoate	[M+H] ⁺ calcd 786; found, 786

Alternate synthesis of Example 53, Bz deprotection:



5

3-[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-8-[[N-methyl(4-fluorobenzene)sulfonamido]methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea (53)

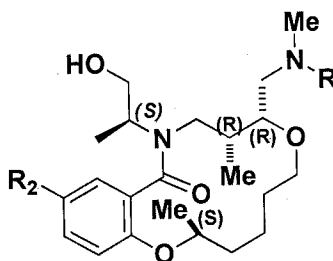
10

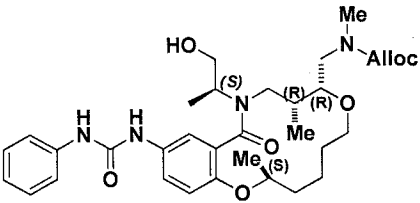
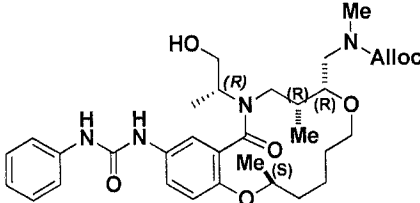
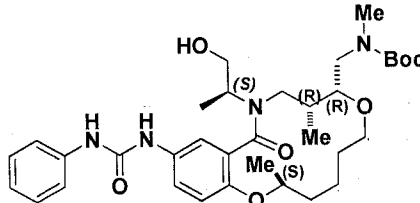
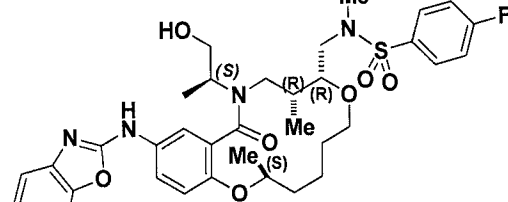
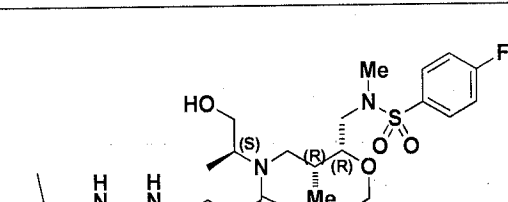
To a solution of Bz-protected alcohol (0.49 g, 0.621 mmol) in methanol (12.42 ml) was added potassium carbonate (0.472 g, 3.42 mmol) under N₂ atmosphere. The suspension was stirred at room temperature for 15h. The reaction mixture was then quenched with Sat. NH₄Cl (15 ml) and extracted with EtOAc. The organic phase was separated, washed with water and brine, dried (Na₂SO₄) and evaporated to dryness. This material was chromatographed on silica, using methanol / dichloromethane to afford the desired product (0.4 g, 94%) as colorless resin. ¹H NMR (300 MHz, CDCl₃) δ 7.95 – 7.51 (m, 3H), 7.39 (m, 1H), 7.34 – 7.07 (m, 5H), 7.07 – 6.91 (m, 1H), 6.91 – 6.60 (m, 2H), 4.65 (s, 1H), 4.33 (s, 1H), 3.93 (m, 4H), 3.56 (m, 2H), 3.10 (m, 2H), 2.96 – 2.55 (m, 5H), 2.47 – 2.27 (m, 1H), 2.04 (m, 1H), 1.64 (m, 3H), 1.47 (m, 4H), 1.38 – 1.22 (m, 2H), 1.22 – 1.09 (m, 3H), 1.09 – 0.90 (m, 2H), 0.79 (m, 2H). MS calculated for C₃₅H₄₅FN₄O₇S [M+H]⁺: 685. Found: 685.

20

The following examples were prepared from this method:

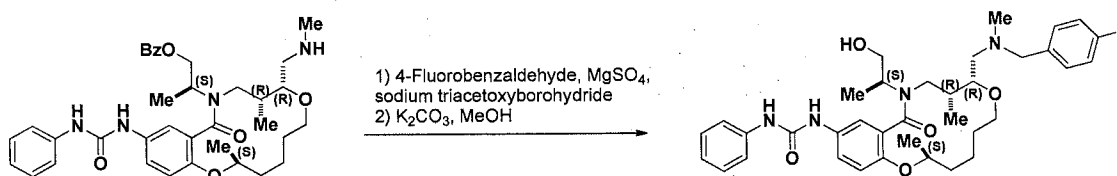
25



No.	Structure	Name	MS
73		prop-2-en-1-yl N-{{(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-12-oxo-14-[(phenylcarbamoyl)amino]-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl)methyl}-N-methylcarbamate	[M+H] ⁺ calcd 611; found, 611
74		prop-2-en-1-yl N-{{(2S,8R,9R)-11-[(2R)-1-hydroxypropan-2-yl]-2,9-dimethyl-12-oxo-14-[(phenylcarbamoyl)amino]-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl)methyl}-N-methylcarbamate	[M+H] ⁺ calcd 611; found, 611
75		tert-butyl N-{{(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-12-oxo-14-[(phenylcarbamoyl)amino]-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl)methyl}-N-methylcarbamate	[M+H] ⁺ calcd 627; found, 627
76		N-{{(2S,8R,9R)-14-[(1,3-benzoxazol-2-yl)amino]-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl)methyl}-4-fluoro-N-methylbenzene-1-sulfonamide	[M+H] ⁺ calcd 683; found, 683
77		3-(dimethyl-1,2-oxazol-4-yl)-1-[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-8-[[N-methyl(4-fluorobenzene)sulfonamido]methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]urea	[M+H] ⁺ calcd 704; found, 704

Synthesis of Example 78:

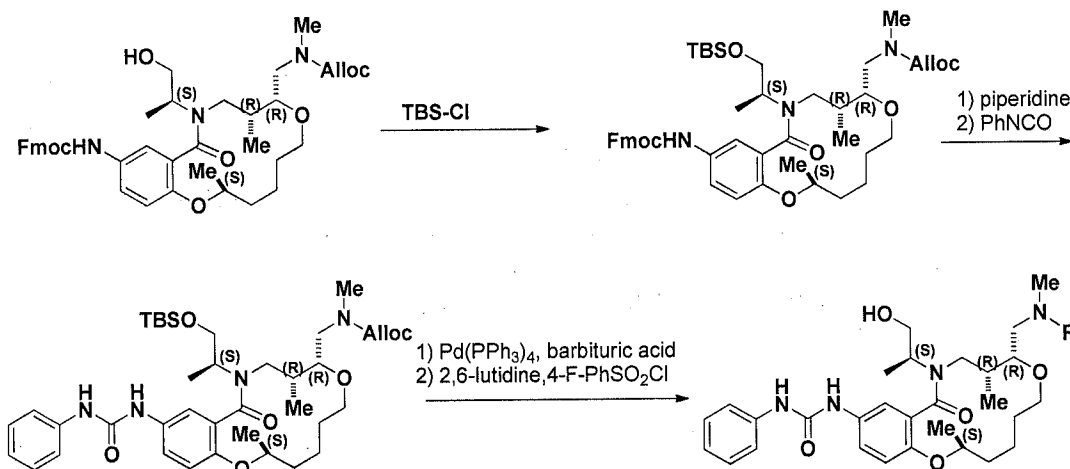
- 127 -



3-[(2R,8R,9R)-8-({[(4-fluorophenyl)methyl](methyl)amino}methyl)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea (78)

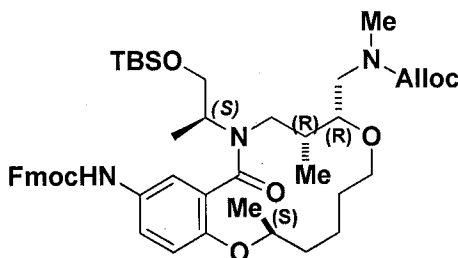
To a mixture of the crude amine (0.0484 g, 0.077 mmol) and magnesium sulfate (7.37 mg, 0.077 mmol) in dry DCM (0.767 ml) was added by 4-fluorobenzaldehyde (0.024 ml, 0.230 mmol) under N₂ atmosphere. The suspension was stirred for 1h followed by the addition of sodium triacetoxyborohydride (0.101 g, 0.537 mmol). The resulting mixture was stirred at room temperature for 4h. The reaction was diluted with DCM (10 ml) and water (10 ml). The aqueous phase was separated and washed with DCM (10 ml). Then the combined organic layers were washed with water (10 ml), separated, dried (Na₂SO₄) and evaporated to dryness. Crude product was carried on to the benzoyl deprotection step, following the same procedure as for 3-[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-8-{[N-methyl(4-fluorobenzene)sulfonamido]methyl}-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea (11 mg (23% over 2 steps) of the desired compound were obtained as colorless resin. ¹H NMR (300 MHz, CDCl₃) δ 8.18 – 7.79 (m, 2H), 7.46 (m, 4H), 7.37 – 7.17 (m, 3H), 7.17 – 6.89 (m, 2H), 6.76 (m, 1H), 4.69 – 4.44 (m, 1H), 4.24 (m, 1H), 3.84 (m, 2H), 3.52 (m, 2H), 3.20 – 3.00 (m, 1H), 2.77 (m, 1H), 2.64 (m, 6H), 2.17 (m, 2H), 2.03 – 1.87 (m, 1H), 1.61 (m, 4H), 1.40 (m, 4H), 1.31 – 1.16 (m, 4H), 1.08 (m, 2H), 0.98 – 0.84 (m, 2H), 0.80 – 0.62 (m, 2H). MS calculated for C₃₆H₄₇FN₄O₅ [M+H]⁺: 635. Found: 635.

Alternative synthesis scheme, protecting group modification (Examples 79-84):



TBS protection:

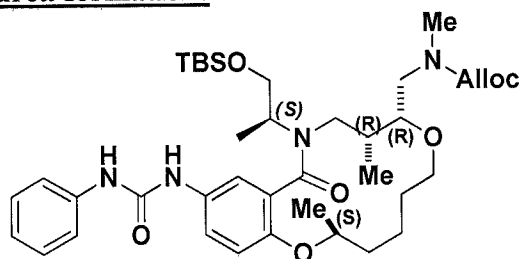
- 128 -



- allyl (((2S,8R,9R)-14-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)-11-((S)-1-
 ((tert-butyldimethylsilyl)oxy)propan-2-yl)-2,9-dimethyl-12-oxo-
 2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-
 yl)methyl)(methyl)carbamate (79):

To a solution of free alcohol (0.494 g, 0.692 mmol) in dry DMF (2.77 ml) was
 added imidazole (0.141 g, 2.076 mmol) followed by TBSCl (0.146 g, 0.692 mmol)
 under N₂ atmosphere at room temperature. The resulting mixture was stirred at
 room temperature for 16 h. The reaction was diluted with DCM (10 ml) and washed
 with water (2 X). The organic phase was then separated, dried (Na₂SO₄) and
 evaporated to dryness. This material was chromatographed on silica, using ethyl
 acetate / hexanes to give 0.37 g (65%) of the desired product. ¹H NMR (300 MHz,
 CDCl₃) δ 7.78 (d, 2H), 7.60 (d, 2H), 7.53 – 7.20 (m, 4H), 7.09 (s, 1H), 6.82 (m, 1H),
 6.55 (s, 1H), 5.94 (m, 1H), 5.47 – 5.06 (m, 1H), 4.75 – 4.39 (m, 4H), 4.26 (m, 1H),
 4.10 (m, 1H), 3.99 – 3.62 (m, 4H), 3.49 – 3.10 (m, 2H), 3.00 (m, 2H), 2.88 – 2.66
 (m, 1H), 2.19 (s, 1H), 2.01 (s, 1H), 1.83 (m, 1H), 1.63 (s, 4H), 1.32 (m, 4H), 1.16 –
 1.02 (m, 2H), 1.02 – 0.57 (m, 9H), 0.15 – -0.15 (m, 5H). MS calculated for
 C₄₇H₆₅N₃O₈ [M+H]⁺: 828. Found: 828.

Fmoc deprotection, urea formation:



- allyl (((2S,8R,9R)-11-((S)-1-((tert-butyldimethylsilyl)oxy)propan-2-yl)-2,9-
 dimethyl-12-oxo-14-(3-phenylureido)-2,3,4,5,6,8,9,10,11,12-
 decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-
 yl)methyl)(methyl)carbamate (80)

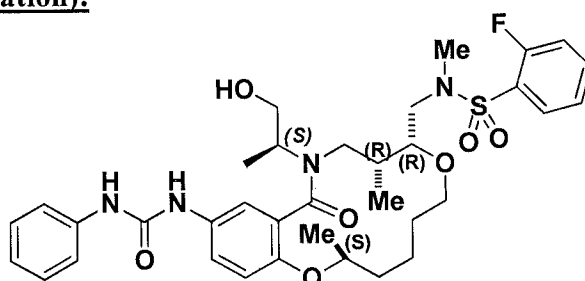
To a solution of Fmoc protected aniline 79 (0.330 g, 0.398 mmol) in dry
 DMF (3.98 ml) was added piperidine (0.079 mL, 0.797 mmol). The reaction
 mixture was stirred for 30 min, then phenyl isocyanate (0.174 mL, 1.594 mmol) was
 added. The resulting mixture was stirred at room temperature for 16 h. The reaction
 was diluted with water and EtOAc, the phases were separated, and the organic phase

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was washed with H₂O 6X. The organic phase was then dried (Na₂SO₄) and evaporated to dryness.

This material was chromatographed on silica, using MeOH / DCM to yield 0.200 g (69%) of the desired product. ¹H NMR (300 MHz, CDCl₃) δ 7.91 (m, 1H), 7.70 (m, 1H), 7.47 (m, 2H), 7.37 – 7.08 (m, 1H), 6.94 (m, 1H), 6.67 (m, 2H), 5.91 (m, 1H), 5.43 – 5.08 (m, 2H), 4.58 (m, 3H), 3.86 (m, 4H), 3.49 (m, 4H), 3.18 – 2.92 (m, 4H), 2.85 (m, 1H), 2.21 (m, 1H), 1.73 (m, 2H), 1.49 (m, 5H), 1.23 (m, 2H), 1.20 – 1.06 (m, 2H), 1.04 – 0.77 (m, 11H), 0.22 – -0.08 (m, 5H). MS calculated for C₃₉H₆₀N₄O₇Si[M+H]⁺: 725. Found: 725.

Preparation of examples 81-84 from example 80 (alloc deprotection sulfonamide formation):



2-fluoro-N-(((2S,8R,9R)-11-((S)-1-hydroxypropan-2-yl)-2,9-dimethyl-12-oxo-14-(3-phenylureido)-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)-N-methylbenzenesulfonamide (81)

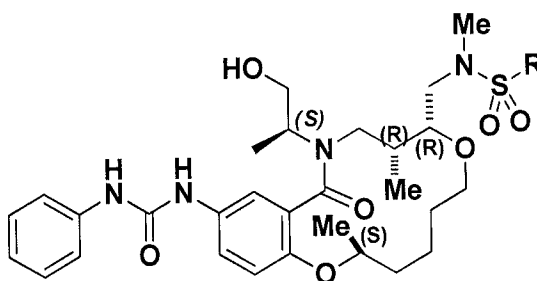
To a solution of alloc protected amine 81 (0.157 g, 0.217 mmol) in DCM (2.5 mL) under N₂ was added 1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (0.483 g, 3.09 mmol) followed by Pd(PPh₃)₄ (0.143 mg, 0.124 mmol). The reaction mixture was stirred for 30 min, then purification via siliabond catch and release was performed to yield product of the TBS deprotection. A small portion of this crude material was purified by HPLC to yield material for biological assay. The crude material was dissolved in DCM (2.5 mL) and to this solution was added 2,6-lutidine (43 uL, 0.373 mmol) followed by 2-fluorobenzene-1-sulfonyl chloride (31 mg, 0.16 mmol). The reaction mixture was stirred 16 h. Purification of the crude mixture was accomplished with SiO₂ chromatography to yield 10.3 mg (12% yield) of desired product. ¹H NMR (300 MHz, CDCl₃) δ 8.01 – 7.71 (m, 2H), 7.71 – 7.48 (m, 3H), 7.39 (m, 1H), 7.37 – 7.10 (m, 3H), 7.10 – 6.86 (m, 2H), 6.86 – 6.63 (m, 1H), 4.64 (s, 1H), 4.40 (m, 1H), 4.22 – 4.03 (m, 1H), 3.91 (m, 3H), 3.76 (m, 1H), 3.65 – 3.39 (m, 2H), 3.32 (m, 1H), 3.09 (m, 1H), 2.99 – 2.71 (m, 4H), 2.67 (m, 1H), 2.04 (m, 1H), 1.90 – 1.59 (m, 4H), 1.47 (m, 4H), 1.39 – 1.22 (m, 2H), 1.22 – 1.09 (m, 2H), 1.08 – 0.89 (m, 2H), 0.77 (d, 2H). MS calculated for C₃₅H₄₅FN₄O₇S [M+H]⁺: 685. Found: 685.

A small aliquot of the intermediate was purified via HPLC for screening.

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No.	Structure	Name	MS
82		3-[(2S,8S,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-8-[(methylamino)methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	[M+H] ⁺ calcd 527; found, 527

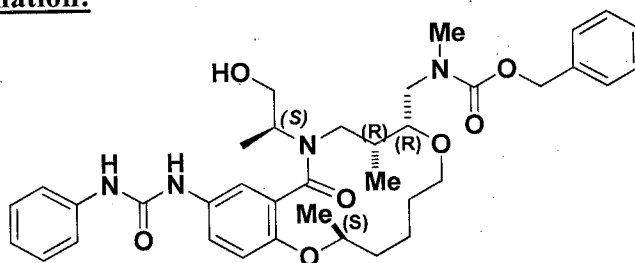
The following examples were prepared from this method:



No.	Structure	Name	MS
83		3-[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-8-[[N-methyl(3-fluorobenzene)sulfonamido]methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	[M+H] ⁺ calcd 685; found, 685
84		3-[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-8-[(N-methylpyridine-3-sulfonamido)methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	[M+H] ⁺ calcd 668; found, 668

5

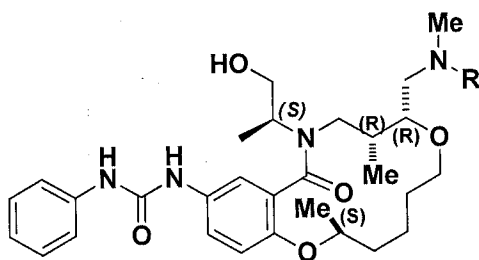
Carbamate formation:



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benzyl(((2S,8R,9R)-11-((S)-1-hydroxypropan-2-yl)-2,9-dimethyl-12-oxo-14-(3-phenylureido)-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)(methyl)carbamate (85)

5 A solution of the crude alloc-protected mixture (19 mg, 0.036 mmol) in dioxane (0.9 mL) was added a solution of NaHCO₃ (0.018 g, 0.219 mmol) in H₂O (0.18 mL) followed by benzyl chloroformate (10 uL, 0.073 mmol). The reaction mixture was stirred overnight. The mixture was then diluted with EtOAc, H₂O, the phases
10 separated and the combined organic phases were washed with H₂O and brine. After drying (Na₂SO₄) the organic phase was concentrated and purified by prep HPLC to yield 4.9 mg (20%) of the desired product. ¹H NMR (300 MHz, CDCl₃) δ 8.02 (s, 1H), 7.67 (m, 2H), 7.49 – 7.15 (m, 6H), 6.97 (m, 2H), 6.87 – 6.56 (m, 2H), 5.09 (m, 2H), 4.65 (s, 1H), 4.43 (m, 1H), 3.82 (m, 4H), 3.53 (m, 3H), 3.28 (m, 1H), 3.07 (m,
15 2H), 2.96 (m, 4H), 2.65 (m, 1H), 1.78 (m, 1H), 1.67 – 1.24 (m, 9H), 1.24 – 0.88 (m, 4H), 0.81 (s, 1H), 0.66 (s, 1H). MS calculated for C₃₇H₄₈N₄O₇ [M+H]⁺: 660. Found: 660.



20

The following compound was prepared from the same method:

No.	Structure	Name	MS
86		propyl N-(((2S,8R,9R)-11-((S)-1-hydroxypropan-2-yl)-2,9-dimethyl-12-oxo-14-((phenylcarbamoyl)amino)-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl)methyl)-N-methylcarbamate	[M+H] ⁺ calcd 613; found, 613

25

Alternate synthesis of analogs, changing reaction order:

Intermediate NN (from Example 79):

To a solution of alloc protected amine **79** (0.225 g, 0.217 mmol) in DCM (3.9 mL) under N₂ was added 1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (0.318 g, 2.038 mmol) followed by Pd(PPh₃)₄ (0.094 g, 0.082 mmol). The reaction mixture was stirred for 1h, then diluted with DCM and washed with sat. NaHCO₃ 3X, H₂O 3X, dried (Na₂SO₄) and solvent evaporated to yield a red oil. The crude material was dissolved in DCM (5.4 mL) and to this solution was added 2,6-lutidine (0.32 mL, 2.7 mmol) followed by 4-fluorobenzene-1-sulfonyl chloride (264 mg, 1.36 mmol). The reaction mixture was stirred 16 h. Purification of the crude mixture was accomplished with SiO₂ chromatography to yield 130 mg (53% yield) of desired product. ¹H NMR (300 MHz, CDCl₃) δ 7.84 – 7.72 (m, 2H), 7.71-7.63 (m, 2H), 7.54 (s, 1H), 7.23-6.92 (m, 8H), 6.77-6.68 (m, 2H), 6.64-6.58 (m, 1H), 4.73-4.41 (m, 2H), 3.96-3.60 (m, 8H), 3.57-3.34 (m, 3H), 3.16-2.82 (m, 2H), 2.80 s, 3H), 2.74 – 2.62 (m, 1H), 2.26-2.04 (m, 1H), 1.93-1.76 (m, 2H), 1.75-1.42 (m, 4H), 1.38 – 1.19 (m, 4H), 1.03 – 0.76 (m, 15H), 0.10—0.06 (m, 6H). MS calculated for C₄₉H₆₄FN₃O₈SSi [M+H]⁺: 902. Found: 902.

1) piperidine
2) acylation
3) TBAF

To a solution of Fmoc protectec aniline NN (0.111 g, 0.123 mmol) in dry DMF (1.2 ml) was added piperidine (0.024 mL, 0.246 mmol). The reaction mixture was stirred for 1h, then quenched with sat. NH₄Cl, extracted into DCM, then the organic phase was dried (Na₂SO₄) and evaporated to dryness. The crude material

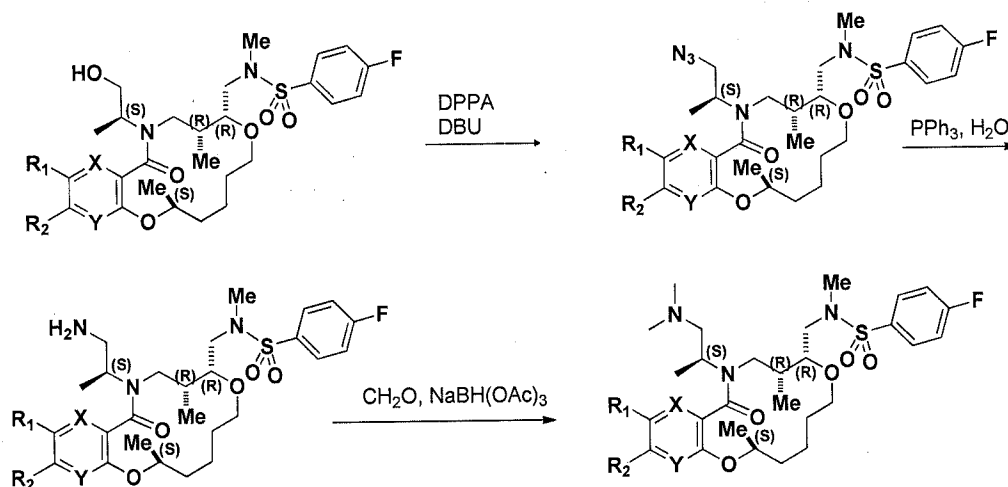
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- (30.7 mg, 0.045 mmol) was either carried on to the TBAF step directly, or dissolved in DCM (0.45 mL) and to this was added DIEA (47 μ L, 0.271 mmol) followed by acetic acid (8 μ L, 0.14 mmol). Then PyBop (70 mg, 0.135 mmol) was added and the mixture stirred for 16 h. The mixture was then diluted with DCM and H₂O, washed aq. with DCM and washed organics with H₂O, dried (Na₂SO₄) and solvent evaporated. The crude material was then dissolved in THF (0.35 mL) and to this was added TBAF in THF (1M, 170 μ L, 0.170 mmol). The mixture was stirred for 16 h, then quenched with sat. NH₄Cl, washed with EtOAc 2X, washed organics with H₂O, brine, dried (Na₂SO₄). Purification was accomplished with prep HPLC to yield 9 mg (43%) of product. ¹H NMR (300 MHz, CDCl₃) δ 7.94 – 7.67 (m, 1H), 7.50 (m, 1H), 7.38 – 7.03 (m, 4H), 6.92 (m, 1H), 4.96 (s, 1H), 4.72 (s, 1H), 4.49 (m, 1H), 4.02 (m, 1H), 3.94 – 3.65 (m, 2H), 3.58 (m, 2H), 3.17 – 2.97 (m, 1H), 2.91 (m, 1H), 2.72 (m, 1H), 2.58 (m, 3H), 2.38 (m, 1H), 2.15 (m, 1H), 1.83 (m, 1H), 1.59 (m, 10H), 1.48 – 1.35 (m, 2H), 1.35 – 1.15 (m, 2H), 1.04 (m, 2H), 0.77 (m, 2H). MS calculated for C₃₀H₄₂FN₃O₇S [M+H]⁺: 608. Found: 608.

The following example was also prepared with this method

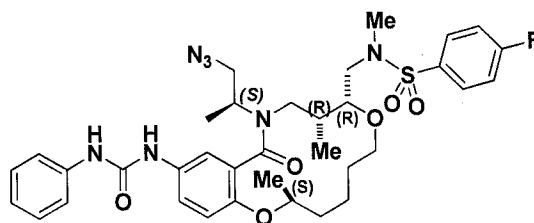
No.	Structure	Name	MS
88		N-[(2S,8R,9R)-14-amino-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl]methyl]-4-fluoro-N-methylbenzene-1-sulfonamide	[M+H] ⁺ calcd 566; found, 566

Exocyclic chain modifications, general synthetic scheme:



Azide formation:

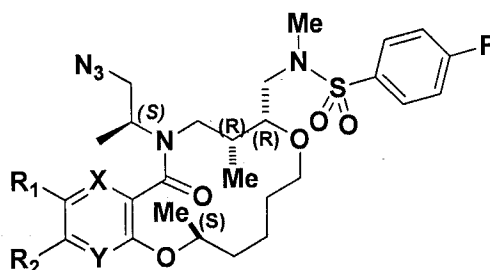
- 134 -



N-(((2S,8R,9R)-11-((S)-1-azidopropan-2-yl)-2,9-dimethyl-12-oxo-14-(3-phenylureido)-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)-4-fluoro-N-methylbenzenesulfonamide (89)

To a solution of 4-fluoro-N-(((2S,8R,9R)-11-((S)-1-hydroxypropan-2-yl)-2,9-dimethyl-12-oxo-14-(3-phenylureido)-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)-N-methylbenzenesulfonamide (0.401 g, 0.586 mmol) in dry THF (2.93 ml) under N₂ was added DBU (0.27 ml, 1.76 mmol) followed by diphenyl phosphorazidate (0.19 ml, 0.88 mmol). The reaction was stirred at rt for 16h. The reaction solvent was evaporated under reduced pressure to afford crude material which was purified by column chromatography using MeOH/DCM to afford the desired product (360 mg, 87%). ¹HNMR (300 MHz, CDCl₃) δ 8.24–7.64 (m, 2H), 7.57–7.33 (m, 2H), 7.31–7.05 (m, 4H), 7.03–6.77 (m, 3H), 6.77–6.53 (m, 1H), 4.67–4.27 (m, 3H), 4.23–4.09 (m, 1H), 4.01–3.84 (m, 2H), 3.83–3.61 (m, 4H), 3.61–3.29 (m, 2H), 3.25–3.02 (m, 2H), 3.06–2.55 (m, 4H), 2.27–1.94 (m, 1H), 1.92–1.32 (m, 6H), 1.30–1.14 (m, 3H), 1.14–1.01 (m, 2H), 0.98–0.85 (m, 1H), 0.83–0.62 (m, 1H). MS (ESI) calcd for C₃₅H₄₄FN₇O₆S [M + H]⁺: 710. Found: 710.

The following examples **90-93** and intermediates OO-PP were prepared from this method:

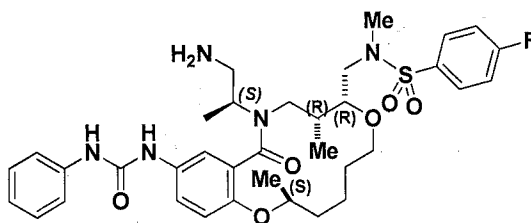


No.	Structure	Name	MS
90		N-(((2S,8R,9R)-11-((S)-1-azidopropan-2-yl)-14-fluoro-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl)methyl)-4-fluoro-N-methylbenzene-1-sulfonamide	[M+H] ⁺ calcd 594; found, 594

No.	Structure	Name	MS
91		N-{[(2S,8R,9R)-11-[(2S)-1-azidopropan-2-yl]-14-cyano-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl]methyl}-4-fluoro-N-methylbenzene-1-sulfonamide	[M+H] ⁺ calcd 601; found, 601
92		N-{[(6S,12R,13R)-15-[(2S)-1-azidopropan-2-yl]-6,13-dimethyl-16-oxo-6H,7H,8H,9H,10H,12H,13H,14H,15H,16H-pyrido[3,2-b]1,9-dioxo-5-azacyclotetradecan-12-yl]methyl}-4-fluoro-N-methylbenzene-1-sulfonamide	[M+H] ⁺ calcd 577; found, 577
93		N-{[(2S,8R,9R)-11-[(2S)-1-azidopropan-2-yl]-2,9-dimethyl-12-oxo-15-(trifluoromethyl)-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl]methyl}-4-fluoro-N-methylbenzene-1-sulfonamide	[M+H] ⁺ calcd 644; found, 644
OO		N-(((2S,8R,9R)-11-((S)-1-azidopropan-2-yl)-2,9-dimethyl-12-oxo-14-(trifluoromethyl)-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)-4-fluoro-N-methylbenzenesulfonamide	[M+H] ⁺ calcd 644; found, 644
PP		N-(((8R,9R)-11-((S)-1-azidopropan-2-yl)-14-(3-(3,5-dimethylisoxazol-4-yl)ureido)-9-methyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)-4-fluoro-N-methylbenzenesulfonamide	[M+H] ⁺ calcd 715; found, 715

Reduction of azide to amine:

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N-(((2S,8R,9R)-11-((S)-1-aminopropan-2-yl)-2,9-dimethyl-12-oxo-14-(3-phenylureido)-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)-4-fluoro-N-methylbenzenesulfonamide (94)

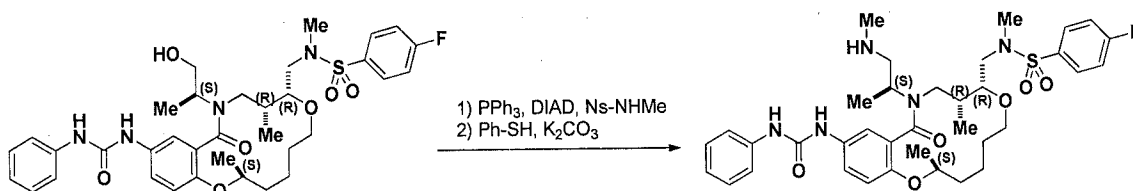
To a solution of N-(((2S,8R,9R)-11-((S)-1-azidopropan-2-yl)-2,9-dimethyl-12-oxo-14-(3-phenylureido)-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)-4-fluoro-N-methylbenzenesulfonamide (0.33 g, 0.465 mmol) in THF (14.64 ml) under N₂ was added Water (0.861 ml) followed by triphenylphosphine (0.305 g, 1.162 mmol). The reaction mixture was stirred for 16h at rt. The reaction was diluted EtOAc, dried (Na₂SO₄) and solvent evaporated to afford a crude material. This material was purified by column chromatography using MeOH/DCM to afford the desired product (45 mg, 76%). ¹H NMR (300 MHz, CDCl₃) δ 8.96–8.20 (m, 2H), 7.92–7.65 (m, 2H), 7.58–7.33 (m, 2H), 7.33–7.05 (m, 4H), 7.08–6.85 (m, 1H), 6.84–6.62 (m, 1H), 4.73–4.32 (m, 1H), 4.16–3.53 (m, 4H), 3.48–3.24 (m, 1H), 3.21–2.92 (m, 4H), 2.91–2.79 (m, 2H), 2.80–2.51 (m, 4H), 2.31–1.89 (m, 2H), 1.89–1.37 (m, 6H), 1.37–1.14 (m, 6H), 1.10–0.89 (m, 2H), 0.67–0.32 (m, 2H). MS (ESI) calcd for Chemical Formula: C₃₅H₄₆FN₅O₆S [M + H]⁺:684. Found: 684.

The following intermediate was prepared using this method.

No.	Structure	Name	MS
QQ		N-(((8R,9R)-11-((S)-1-aminopropan-2-yl)-14-(3-(3,5-dimethylisoxazol-4-yl)ureido)-9-methyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)-4-fluoro-N-methylbenzenesulfonamide	[M+H] ⁺ calcd 689; found, 689

Alternative preparation of amines:

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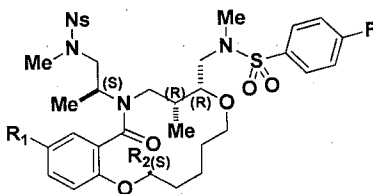


3-[(2S,8R,9R)-2,9-dimethyl-8-[[N-methyl(4-fluorobenzene)sulfonamido]methyl]-11-[(2S)-1-(methylamino)propan-2-yl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea (95)

To a solution of free alcohol (0.081 g, 0.118 mmol) in dry THF (2.366 ml) was added triphenylphosphine (0.155 g, 0.591 mmol) and N-methyl-2-nitrobenzenesulfonamide (0.051 g, 0.237 mmol) under N₂ atmosphere at room temperature. This stirring solution was then cooled to 0°C and DIAD (0.115 ml, 0.591 mmol) was added. The resulting mixture was stirred for 15h, letting slowly warm to room temperature. The reaction was concentrated in vacuo, then crude product was re-dissolved in dry DMF (0.672 ml) and potassium carbonate (0.030 g, 0.215 mmol) was introduced to the reaction mixture, followed by benzenethiol (0.011 ml, 0.108 mmol). The resulting mixture was stirred under Ar at room temperature for 15h.

This material was then evaporated to dryness and chromatographed on silica, using methanol / dichloromethane to give 2.9 mg (4%) of the desired compound. ¹H NMR (300 MHz, CDCl₃) δ 8.10 (d, 2H), 7.95 – 7.67 (m, 3H), 7.59 (d, 1H), 7.40 (m, 2H), 7.33 – 7.05 (m, 2H), 6.95 (m, 1H), 6.70 (m, 1H), 4.61 (s, 1H), 4.37 – 3.97 (m, 1H), 3.97 – 3.72 (m, 2H), 3.64 (m, 2H), 3.31 – 3.09 (m, 2H), 2.99 (m, 2H), 2.85 (m, 1H), 2.74 (m, 4H), 2.45 (m, 4H), 1.97 (s, 2H), 1.71 (m, 2H), 1.50 (m, 2H), 1.36 (m, 3H), 1.18 (m, 4H), 0.96 (m, 2H), 0.66 (m, 2H). MS calculated for C₃₆H₄₈FN₅O₆S [M+H]⁺: 698. Found: 698.

The following intermediates **RR-TT** were isolated from the first step with this method:

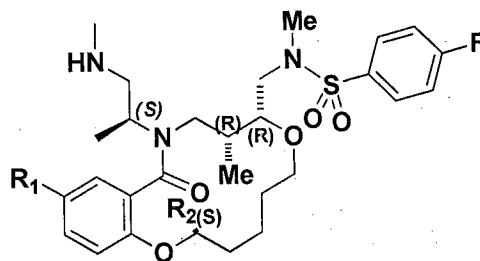


30

No.	Structure	Name	MS
RR		N-((R)-2-((2S,8R,9R)-8-((4-fluoro-N-methylphenylsulfonamido)methyl)-2,9-dimethyl-12-oxo-14-(3-phenylureido)-3,4,5,6,9,10-hexahydrobenzo[b][1,9,5]di-oxaazacyclotetradecin-	[M+H] ⁺ calcd 817; found, 817

No.	Structure	Name	MS
		11(2H,8H,12H)-yl)propyl)-N-methyl-2-nitrobenzenesulfonamide	
SS		N-((S)-2-((2S,8R,9R)-14-fluoro-8-((4-fluoro-N-methylphenylsulfonamido)methyl)-2,9-dimethyl-12-oxo-3,4,5,6,9,10-hexahydrobenzo[b][1,9,5]dioxazacyclotetradecin-11(2H,8H,12H)-yl)propyl)-N-methyl-2-nitrobenzenesulfonamide	[M+H] ⁺ calcd 767; found, 767
TT		N-((R)-2-((8S,9S)-14-(3-(3,5-dimethylisoxazol-4-yl)ureido)-8-((4-fluoro-N-methylphenylsulfonamido)methyl)-9-methyl-12-oxo-3,4,5,6,9,10-hexahydrobenzo[b][1,9,5]dioxazacyclotetradecin-11(2H,8H,12H)-yl)propyl)-N-methyl-2-nitrobenzenesulfonamide	[M+H] ⁺ calcd 888; found, 888

The following examples were also prepared with this method:

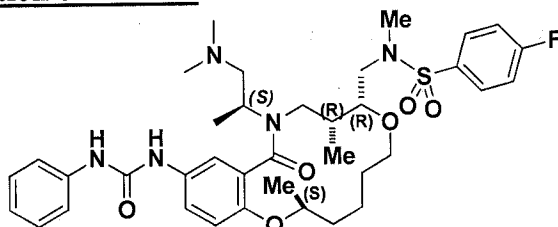


5

No.	Structure	Name	MS
96		3-[(2S,8R,9R)-2,9-dimethyl-8-{[N-methyl(4-fluorobenzene)sulfonamido]methyl}-11-[(2R)-1-(methylamino)propan-2-yl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	[M+H] ⁺ calcd 698; found, 698

No.	Structure	Name	MS
97		N-(((2S,8R,9R)-2,9-dimethyl-11-((2S)-1-(methylamino)propan-2-yl)-12-oxo-14-(trifluoromethyl)-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl)methyl)-4-fluoro-N-methylbenzene-1-sulfonamide	[M+H] ⁺ calcd 632; found, 632
98		4-fluoro-N-(((2S,8R,9R)-14-fluoro-2,9-dimethyl-11-((2S)-1-(methylamino)propan-2-yl)-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl)methyl)-N-methylbenzene-1-sulfonamide	[M+H] ⁺ calcd 582; found, 582
99		N-(((8R,9R)-14-(3-(3,5-dimethylisoxazol-4-yl)ureido)-9-methyl-11-((S)-1-(methylamino)propan-2-yl)-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)-4-fluoro-N-methylbenzenesulfonamide	[M+H] ⁺ calcd 703; found, 703

Reductive methylation of amines:



5

N-(((2S,8R,9R)-11-((S)-1-(dimethylamino)propan-2-yl)-2,9-dimethyl-12-oxo-14-(3-phenylureido)-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)-4-fluoro-N-methylbenzenesulfonamide (100)

- 10 To a solution of N-(((2S,8R,9R)-11-((S)-1-aminopropan-2-yl)-2,9-dimethyl-12-oxo-14-(3-phenylureido)-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)-4-fluoro-N-methylbenzenesulfonamide **94** (39 mg, 0.058 mmol) in DCM (1.154 ml) was added magnesium sulfate (0.069 g, 0.577 mmol) followed by Formaldehyde (0.026 ml, 0.346 mmol). This mixture was stirred for 1h at room temperature. After this
- 15 period sodium triacetoxyborohydride (0.147 g, 0.692 mmol) was added to the reaction flask and the mixture stirred overnight. The reaction solvent was evaporated

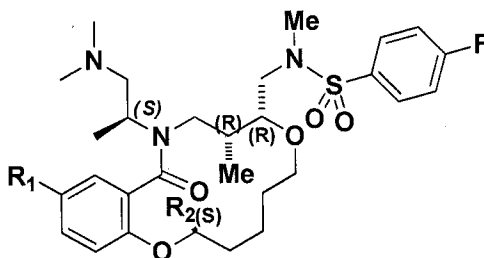
- 140 -

under reduced pressure to afford crude mixture which was purified by column chromatography using MeOH/DCM to afford the desired product (360 mg, 87%).

¹HNMR (300 MHz, CDCl₃) δ 8.24–7.64 (m, 2H), 7.57–7.33 (m, 2H), 7.31–7.05 (m, 4H), 7.03–6.77 (m, 3H), 6.77–6.53 (m, 1H), 4.67–4.27 (m, 3H), 4.23–4.09 (m, 1H), 4.01–3.84 (m, 2H), 3.83–3.61 (m, 4H), 3.61–3.29 (m, 2H), 3.25–3.02 (m, 2H), 3.06–2.55 (m, 4H), 2.27–1.94 (m, 1H), 1.92–1.32 (m, 6H), 1.30–1.14 (m, 3H), 1.14–1.01 (m, 2H), 0.98–0.85 (m, 1H), 0.83–0.62 (m, 1H),. MS (ESI) calcd for Chemical Formula: C₃₇H₅₀FN₅O₆S [M + H]⁺: 712. Found: 712.

The following examples were also prepared with this method starting from

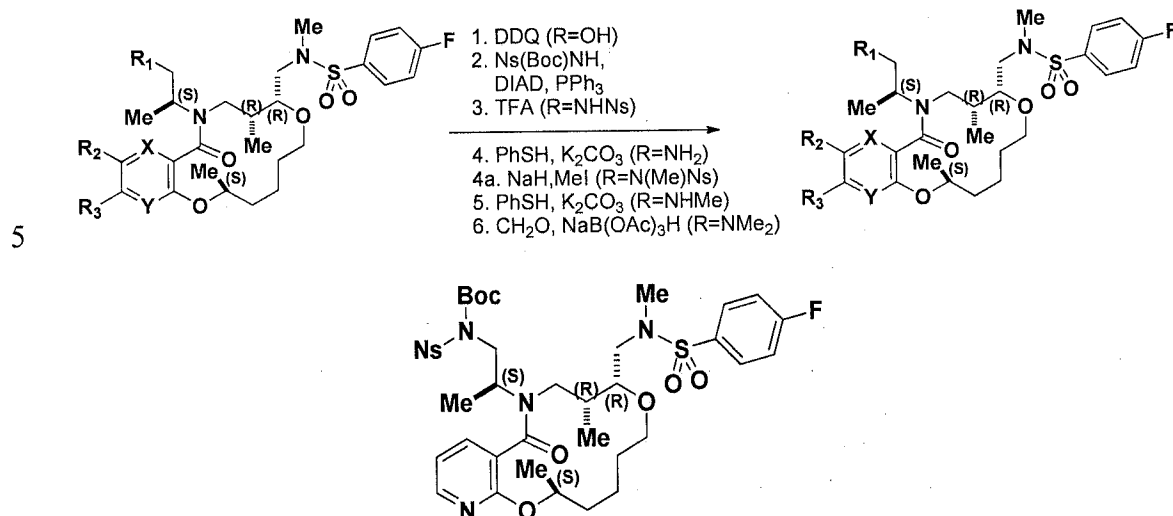
10 Examples 101-105:



No.	Structure	Name	MS
101		N-([(2S,8R,9R)-11-[(2S)-1-(dimethylamino)propan-2-yl]-2,9-dimethyl-12-oxo-14-(trifluoromethyl)-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl]methyl]-4-fluoro-N-methylbenzene-1-sulfonamide	[M+H] ⁺ calcd 646; found, 646
102		N-([(2S,8R,9R)-11-[(2S)-1-(dimethylamino)propan-2-yl]-14-fluoro-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl]methyl]-4-fluoro-N-methylbenzene-1-sulfonamide	[M+H] ⁺ calcd 596; found, 596
103		N-(((2S,8R,9R)-11-((R)-1-(dimethylamino)propan-2-yl)-2,9-dimethyl-12-oxo-14-(3-phenylureido)-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)-4-fluoro-N-methylbenzenesulfonamide	[M+H] ⁺ calcd 712; found, 712

No.	Structure	Name	MS
104		3-(dimethyl-1,2-oxazol-4-yl)-1-[(2S,8R,9R)-11-[(2S)-1-(dimethylamino)propan-2-yl]-2,9-dimethyl-8-{[N-methyl(4-fluorobenzene)sulfonamido]methyl}-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]urea	[M+H] ⁺ calcd 731; found, 731
105		N-(((8R,9R)-11-((S)-1-(dimethylamino)propan-2-yl)-14-(3-(3,5-dimethylisoxazol-4-yl)ureido)-9-methyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)-4-fluoro-N-methylbenzenesulfonamide	[M+H] ⁺ calcd 717; found, 717

Preparation of intermediates UU-ZZ and Examples 106-112 through an alternate synthetic route:



10 **tert-butyl ((S)-2-((8R,9R,15S)-9-((4-fluoro-N-methylphenylsulfonamido)methyl)-8,15-dimethyl-5-oxo-8,9,12,13,14,15-hexahydropyrido[2,3-b][1,9,5]dioxazacyclotetradecin-6(5H,7H,11H)-yl)propyl)((2-nitrophenyl)sulfonyl)carbamate (UU)**

To a solution of triphenylphosphine (0.041 g, 0.155 mmol) in 0.69 mL THF at 0 °C was added diisopropyl azodicarboxylate (DIAD, 0.030 mL, 0.155 mmol). After stirring was continued for 10 minutes at reduced temperature, N-(tert-Butoxycarbonyl)-2-nitrobenzenesulfonamide (0.050 g, 0.165 mmol) was added as a

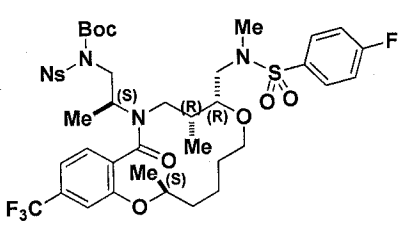
15

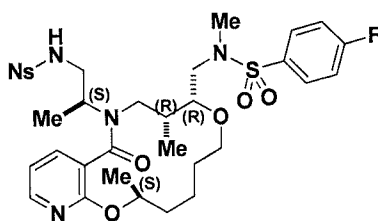
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solid in one portion followed by a solution of primary alcohol **55** (0.057g, 0.103 mmol) in 0.34 mL THF. Stirring was continued at reduced temperature for 15 minutes at which time the icebath was removed and the reaction was allowed to warm to room temperature. After one hour the SM was consumed by LC/MS analysis and the reaction was concentrated to an oil. Purification by flash column chromatography (20% EA/hexanes - 100% EA) gave 50.0 mg of pure product (58% yield).

¹H NMR (300 MHz, CDCl₃) δ 8.35 – 8.18 (m, 1H), 8.18 – 8.07 (m, 1H), 7.88 – 7.58 (m, *J* = 24.9, 5H), 7.41 – 7.07 (m, 2H), 6.97 – 6.77 (m, 1H), 5.66 – 5.06 (m, 1H), 4.75 – 4.05 (m, 1H), 4.07 – 3.37 (m, 4H), 3.32 – 3.04 (m, 1H), 3.03 – 2.56 (m, 5H), 2.54 – 2.12 (m, 1H), 2.09 – 1.92 (m, 1H), 1.88 – 1.02 (m, 22H), 0.96 – 0.70 (m, 3H). MS (ESI) calcd for C₃₈H₅₀FN₅O₁₁S₂ [M + H]⁺: 836. Found: 836.

The following intermediate was also prepared using this method:

No.	Structure	Name	MS
VV		tert-butyl ((S)-2-((2S,8R,9R)-8-((4-fluorophenyl)sulfonyl)propyl)-2,9-dimethyl-12-oxo-15-(trifluoromethyl)-3,4,5,6,9,10-hexahydrobenzo[b][1,9,5]dioxazacyclotetradecin-11(2H,8H,12H)-yl)propyl)-2-nitrophenyl)sulfonyl)carbamate	[M+H] ⁺ calcd 903; found, 903



N-(((8R,9R,15S)-8,15-dimethyl-6-(((S)-1-(2-nitrophenyl)sulfonyl)propyl)-5-oxo-5,6,7,8,9,11,12,13,14,15-decahydropyrido[2,3-b][1,9,5]dioxazacyclotetradecin-9-yl)methyl)-4-fluoro-N-methylbenzenesulfonamide (WW)

To a solution of carbamate in 0.6 mL of dichloromethane was added 0.15 mL trifluoroacetic acid. The reaction was stirred at r.t. for 90 minutes at which time no SM was observed by lc/ms. Solvent was then removed and the remaining oil was azeotroped with 3 x 2 mL toluene before being used in the next reaction crude.

¹H NMR (300 MHz, CDCl₃) δ 8.30 – 8.04 (m, 2H), 7.92 – 7.54 (m, 5H), 7.25 – 7.09 (m, *J* = 1.2, 4H), 6.96 – 6.84 (m, 1H), 6.17 – 5.96 (m, 1H), 5.70 – 5.44 (m, 1H), 3.94

– 3.56 (m, 4H), 3.54 – 3.31 (m, 2H), 3.29 – 2.85 (m, 4H), 2.80 (s, 3H), 1.99 – 1.43 (m, 6H), 1.40 – 1.03 (m, 6H), 1.01 – 0.61 (m, 4H). MS (ESI) calcd for $C_{33}H_{42}FN_5O_9S_2$ $[M + H]^+$: 736. Found: 736.

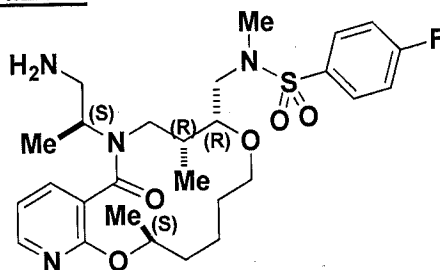
5

The following intermediate was also prepared using this method:

No.	Structure	Name	MS
XX		N-(((2S,8R,9R)-2,9-dimethyl-11-((S)-1-(2-nitrophenylsulfonamido)propan-2-yl)-12-oxo-15-(trifluoromethyl)-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)-4-fluoro-N-methylbenzenesulfonamide	$[M+H]^+$ calcd 803; found, 803

10

Formed through Nosyl-amine

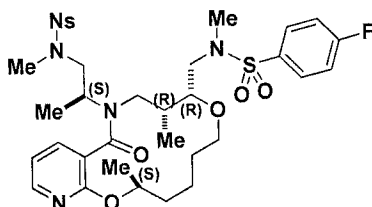


15 N-(((8R,9R,15S)-6-((S)-1-aminopropan-2-yl)-8,15-dimethyl-5-oxo-5,6,7,8,9,11,12,13,14,15-decahydropyrido[2,3-b][1,9,5]dioxazacyclotetradecin-9-yl)methyl)-4-fluoro-N-methylbenzenesulfonamide (106)

Brought sulfonamide N-(((8R,9R,15S)-8,15-dimethyl-6-((S)-1-(2-nitrophenylsulfonamido)propan-2-yl)-5-oxo-5,6,7,8,9,11,12,13,14,15-decahydropyrido[2,3-b][1,9,5]dioxazacyclotetradecin-9-yl)methyl)-4-fluoro-N-methylbenzenesulfonamide (0.012 g, 0.016 mmol) up in 0.16 mL of DMF. Added potassium carbonate (9.02 mg, 0.065 mmol) followed by Thiophenol (3.36 μ L, 0.033 mmol), turned yellow immediately. Continued stirring at r.t. for 90 minutes at which time the reaction was then diluted with ~ 1 mL water and extracted with 2 x 2 mL ethyl acetate. The combined organics were then dried over sodium sulfate and concentrated. Purification with flash chromatography followed using MeOH/DCM to afford the desired product (22 mg, 44%). 1H NMR (300 MHz, $CDCl_3$) 1H NMR (300 MHz, $CDCl_3$) δ 8.17–8.01 (m, 1H), 7.87–7.57 (m, 2H), 7.49–7.27 (m, 1H), 7.19–7.04 (m, 2H), 6.97–6.64 (m, 1H), 5.59–5.10 (m, 2H), 4.08–3.30 (m, 4H), 3.20–2.79 (m, 3H), 2.78–2.56 (m, 3H), 2.48–2.15 (m, 2H), 2.13–1.89 (m, 3H), 1.86–1.64 (m, 2H), 1.64–1.29 (m, 4H), 1.29–1.11 (m, 3H), 1.10–0.74 (m, 3H), 0.72–0.33 (m, 4H). MS (ESI) calcd for $C_{27}H_{39}FN_4O_5S$ $[M + H]^+$: 551. Found: 551.

The following example was prepared using this method:

No.	Structure	Name	MS
107		N-(((2S,8R,9R)-11-((S)-1-aminopropan-2-yl)-2,9-dimethyl-12-oxo-15-(trifluoromethyl)-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)-4-fluoro-N-methylbenzenesulfonamide	[M+H] ⁺ calcd 618; found, 618

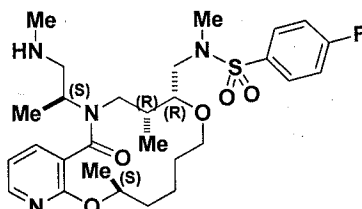


- 5 N-((S)-2-((8R,9R,15S)-9-((4-fluoro-N-methylphenylsulfonamido)methyl)-8,15-dimethyl-5-oxo-8,9,12,13,14,15-hexahydropyrido[2,3-b][1,9,5]dioxazacyclotetradecin-6(5H,7H,11H)-yl)propyl)-N-methyl-2-nitrobenzenesulfonamide (YY)
- 10 To a solution of **WW** (0.035 g, 0.048 mmol) in 0.48 mL DMF was added potassium carbonate (0.033 g, 0.238 mmol) followed by methyl iodide (3.57 μ L, 0.057 mmol). The reaction was stirred at r.t. for 1 hour at which time no SM remained by lc/ms. A quench followed, 3 mL saturated ammonium chloride solution and the reaction was extracted with 2 x 10 mL DCM. The combined organics were dried over Na₂SO₄
- 15 and concentrated. The crude oil was then purified by chromatography 10-60% EA/hex to yield 25.0 mg (70%).
- ¹H NMR (300 MHz, CDCl₃) 8.20 – 8.07 (m, 1H), 7.93 – 7.86 (m, 1H), 7.82 – 7.41 (m, 6H), 7.25 – 7.06 (m, 2H), 6.98 – 6.79 (m, 1H), 5.68 – 5.06 (m, 1H), 4.18 – 3.96 (m, 1H), 3.96 – 3.68 (m, 3H), 3.67 – 3.52 (m, 1H), 3.26 – 3.07 (m, 1H), 3.04 – 2.72 (m, 12H), 1.91 – 1.15 (m, 9H), 1.12 – 0.83 (m, 2H), 0.75 (d, *J* = 6.5, 2H).
- 20 MS (ESI) calcd for C₃₄H₄₄FN₅O₉S₂ [M + H]⁺:750. Found: 750.

The following intermediate was prepared using this method:

No.	Structure	Name	MS
ZZ		N-((S)-2-((2S,8R,9R)-8-((4-fluoro-N-methylphenylsulfonamido)methyl)-2,9-dimethyl-12-oxo-15-(trifluoromethyl)-3,4,5,6,9,10-hexahydrobenzo[b][1,9,5]dioxazacyclotetradecin-11(2H,8H,12H)-yl)propyl)-N-methyl-2-nitrobenzenesulfonamide	[M+H] ⁺ calcd 817; found, 817

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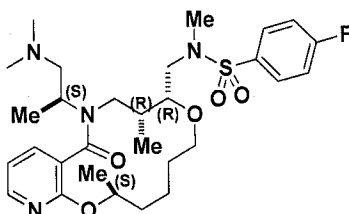
- 5 **N-(((8R,9R,15S)-8,15-dimethyl-6-((S)-1-(methylamino)propan-2-yl)-5-oxo-5,6,7,8,9,11,12,13,14,15-decahydropyrido[2,3-b][1,9,5]dioxazacyclotetradecin-9-yl)methyl)-4-fluoro-N-methylbenzenesulfonamide (108)**

10 To a solution of methyl sulfonamide (0.025 g, 0.033 mmol) in 0.33 mL DMF was added potassium carbonate (0.023 g, 0.167 mmol) followed by thiophenol (6.87 μ L, 0.067 mmol). Continued stirring at rt for 90 min at which time the reaction was then diluted with $\sim$ 1 mL water and extracted with 2 x 2 mL ethyl acetate. The combined organics were then dried over sodium sulfate and concentrated. Purification with flash chromatography followed (0 – 10% MeOH/DCM). Recovered 12.5 mg product (66% yield).

- 15 ^1H NMR (300 MHz, CDCl_3) δ 8.31 – 8.08 (m, 1H), 7.94 – 7.38 (m, 3H), 7.24 – 7.11 (m, 2H), 7.02 – 6.81 (m, 1H), 5.72 – 5.13 (m, 1H), 4.46 – 3.76 (m, 3H), 3.74 – 3.63 (m, 1H), 3.58 – 3.42 (m, 1H), 3.38 – 3.08 (m, 1H), 3.08 – 2.93 (m, 1H), 2.94 – 2.71 (m, 5H), 2.71 – 2.50 (m, 3H), 2.41 (s, 2H), 2.25 – 1.94 (m, 2H), 1.95 – 1.55 (m, 4H), 1.49 – 1.18 (m, 6H), 1.07 (t, J = 6.4, 3H), 0.78 (d, J = 6.6, 1H).
- 20 MS (ESI) calcd for $\text{C}_{28}\text{H}_{41}\text{FN}_4\text{O}_5\text{S}$ $[\text{M} + \text{H}]^+$: 565. Found: 565.

The following example was prepared using this method:

No.	Structure	Name	MS
109		N-(((2S,8R,9R)-2,9-dimethyl-11-((S)-1-(methylamino)propan-2-yl)-12-oxo-15-(trifluoromethyl)-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)-4-fluoro-N-methylbenzenesulfonamide	$[\text{M} + \text{H}]^+$ calcd 632; found, 632



25

- N-(((8R,9R,15S)-6-((S)-1-(dimethylamino)propan-2-yl)-8,15-dimethyl-5-oxo-5,6,7,8,9,11,12,13,14,15-decahydropyrido[2,3-b][1,9,5]dioxazacyclotetradecin-9-yl)methyl)-4-fluoro-N-methylbenzenesulfonamide (110)**

- 146 -

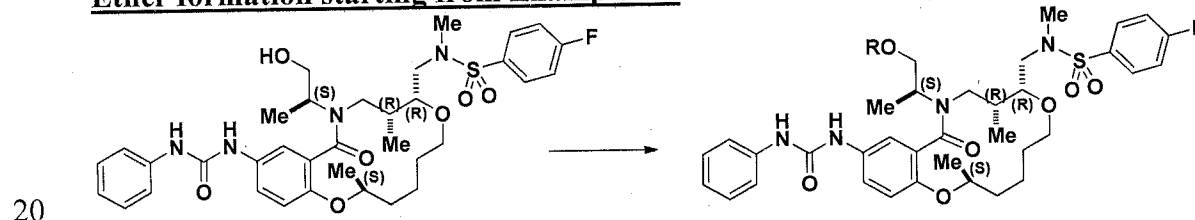
To a solution of secondary amine **108** (10.00 mg, 0.0177 mmol) in 0.35 mL DCM was added magnesium sulfate (0.021 g, 0.177 mmol) followed by 37% formaldehyde (7.91 μ l, 0.106 mmol). Stirred for 1h. Sodium triacetoxymethylborohydride (0.045 g, 0.212 mmol) was subsequently added and stirring was continued overnight. The reaction was then quenched with 1 mL saturated sodium bicarbonate and extracted w 3 x 2 mL DCM. The combined organics were dried over potassium carbonate and concentrated. Column chromatography was then performed (2-15% MeOH/DCM) to give 8.0 mg product (78%). ¹H NMR (300 MHz, CDCl₃) δ 8.21 – 8.04 (m, 1H), 7.85 – 7.63 (m, 2H), 7.62 – 7.33 (m, 1H), 7.17 – 7.05 (m, 2H), 6.90 – 6.73 (m, 1H), 5.60 – 4.99 (m, 1H), 4.27 – 3.46 (m, 4H), 3.42 (s, 2H), 3.21 – 2.84 (m, 2H), 2.85 – 2.65 (m, 3H), 2.64 – 2.09 (m, 5H), 2.04 (s, 3H), 1.97 – 1.10 (m, 10H), 1.07 – 0.55 (m, 5H). MS (ESI) calcd for C₂₉H₄₃FN₄O₅S [M + H]⁺: 579. Found: 579.

No.	Structure	Name	MS
111		N-[(2S,8R,9R)-11-[(2S)-1-(dimethylamino)propan-2-yl]-2,9-dimethyl-12-oxo-15-(trifluoromethyl)-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl)methyl]-4-fluoro-N-methylbenzene-1-sulfonamide	[M+H] ⁺ calcd 646; found, 646
112		N-(((8R,9R,15S)-6-((S)-1-((2,4-difluorobenzyl)(methyl)amino)propan-2-yl)-8,15-dimethyl-5-oxo-5,6,7,8,9,11,12,13,14,15-decahydropyrido[2,3-b][1,9,5]dioxazacyclotetradecin-9-yl)methyl)-4-fluoro-N-methylbenzenesulfonamide	[M+H] ⁺ calcd 691; found, 691

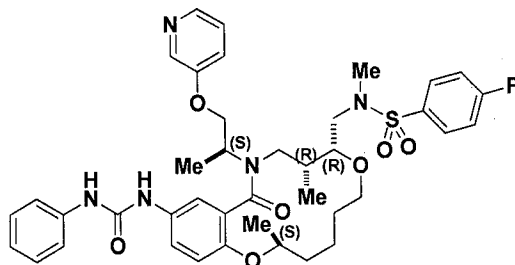
15

*compound 112 was prepared using the same procedure as about expect using 2,5-Difluorobenzaldehyde instead of formaldehyde

Ether formation starting from Example 53:



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N-(((2S,8R,9R)-2,9-dimethyl-12-oxo-14-(3-phenylureido)-11-((S)-1-(pyridin-3-yloxy)propan-2-yl)-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxaza cyclotetradec in-8-yl)methyl)-4-fluoro-N-methylbenzenesulfonamide (113)

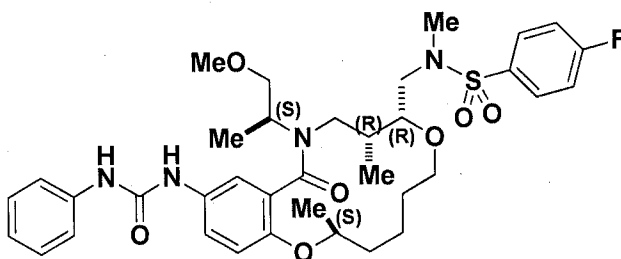
To a solution of triphenylphosphine (0.017 g, 0.066 mmol) in 0.51 mL THF at 0 °C was added diisopropyl azodicarboxylate (DIAD, 0.013 mL, 0.066 mmol). After stirring was continued for 10 minutes at reduced temperature, pyridine-3-ol (6.80 mg, 0.072 mmol) was added followed by a solution of the primary alcohol **33** (0.035 g, 0.051 mmol) in 0.30 mL of THF. Stirring was continued at reduced temperature for 10 minutes at which time the icebath was removed and the reaction was allowed to warm to room temperature. After one hour the SM was consumed by LC/MS analysis and the reaction was concentrated to an oil and was purified by flash column chromatography (40% EA/hexanes - 100% EA) to give 28.1 mg of product (72% yield).

¹H NMR (300 MHz, CDCl₃) δ 8.43 – 8.09 (m, 2H), 7.95 – 7.44 (m, 4H), 7.45 – 7.15 (m, 11H), 7.07 – 6.62 (m, 2H), 4.83 – 4.48 (m, 1H), 4.44 – 3.76 (m, 4H), 3.76 – 3.30 (m, 1H), 3.27 – 2.95 (m, 2H), 2.98 – 2.64 (m, 4H), 2.43 – 1.94 (m, 2H), 1.89 – 1.66 (m, 1H), 1.63 – 1.28 (m, 6H), 1.29 – 1.01 (m, 5H), 0.98 – 0.66 (m, 4H).

MS (ESI) calcd for C₄₀H₄₈FN₅O₇S [M + H]⁺: 762. Found: 762.

The following example was prepared using this method:

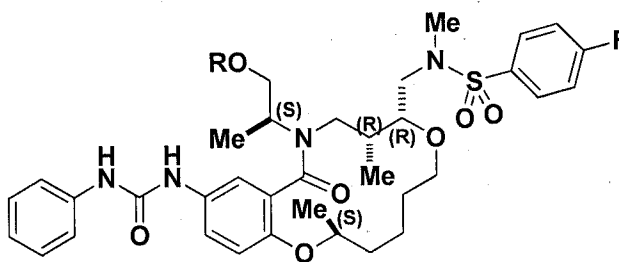
No.	Structure	Name	MS
114		3-[(2S,8R,9R)-2,9-dimethyl-8-{[N-methyl(4-fluorobenzene)sulfonamido]methyl}-12-oxo-11-[(2S)-1-(pyridin-2-yloxy)propan-2-yl]-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	[M+H] ⁺ calcd 762; found, 762



3-[(2S,8R,9R)-11-[(2S)-1-methoxypropan-2-yl]-2,9-dimethyl-8-[[N-methyl(4-fluorobenzene)sulfonamido]methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea (115)

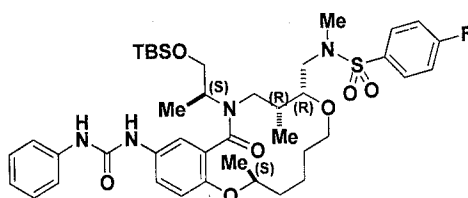
To a solution of free alcohol **53** (15.3 mg, 0.022 mmol) in dry DMF (0.223 ml) was added iodomethane (0.014 mL, 0.223 mmol) under N₂ atmosphere at room temperature. The mixture was cooled to 0°C and sodium hydride (1.787 mg, 0.045 mmol) was added. The resulting mixture was slowly warmed to room temperature and allowed to stir at room temperature for 15h. The reaction was then cooled to 0°C and quenched with Sat. NH₄Cl (10 ml) and the product was extracted with EtOAc (2 X 10 ml). Combined organics were washed with water (4 X 10 ml), brine, dried (Na₂SO₄) and evaporated to dryness to give an oil. This material was chromatographed on silica, using methanol / dichloromethane to give the product (4 mg, 26%) as colorless resin. ¹H NMR (300 MHz, CDCl₃) δ 7.89-7.65 (m, 3H), 7.60-7.41 (m, 2H), 7.31-7.15 (m, 3H), 7.07-6.89 (m, 2H), 6.85-6.70 (m, 2H), 5.38 (m, 1H), 3.90-3.77 (m, 2H), 3.69-3.43 (m, 3H), 3.30 (m, 2H), 3.15 (m, 2H), 2.89 (m, 1H), 2.82 (m, 1H), 2.29-2.11 (m, 1H), 2.07-1.85 (m, 1H), 1.63 (m, 1H), 1.47-1.35 (m, 5H), 1.33-1.16 (m, 8H), 1.11-0.95 (m, 4H), 0.91-0.81 (m, 2H), 0.79-0.70 (m, 1H). MS calculated for C₃₆H₄₇FN₄O₇S [M+H]⁺: 699. Found: 699.

The following examples were prepared using the same method:



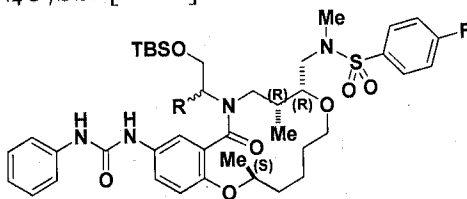
No.	Structure	Name	MS
116		3-[(2S,8R,9R)-11-[(2S)-1-(methoxymethoxy)propan-2-yl]-2,9-dimethyl-8-[[N-methyl(4-fluorobenzene)sulfonamido]methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	[M+H] ⁺ calcd 729; found, 729

No.	Structure	Name	MS
117		3-[(2S,8R,9R)-11-[(2S)-1-[(2-methoxyethoxy)methoxy]propan-2-yl]-2,9-dimethyl-8-{{[N-methyl(4-fluorobenzene)sulfonamido]methyl}-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	[M ⁺ H] ⁺ calcd 773; found, 773



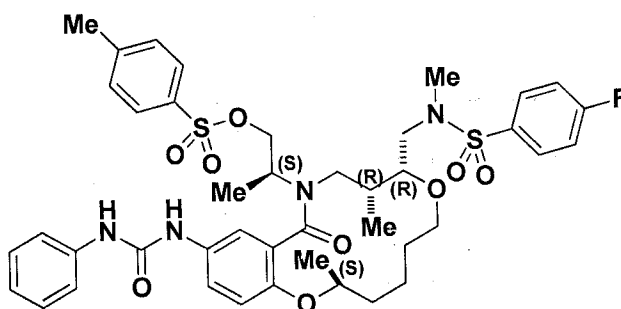
5 **3-[(2S,8R,9R)-11-[(2S)-1-[(tert-butyldimethylsilyl)oxy]propan-2-yl]-2,9-dimethyl-8-{{[N-methyl(4-fluorobenzene)sulfonamido]methyl}-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea (118)**

To a solution of alcohol **53** (0.021 g, 0.031 mmol) in dry DMF (0.123 ml) was added 1H-imidazole (6.26 mg, 0.092 mmol), followed by *tert*-butylsilane (9.24 mg, 0.061 mmol) under N₂ atmosphere. The resulting mixture was stirred at room temperature for 15h. The reaction was diluted with DCM (1 ml) and water (0.5 ml). The organic phase was separated, and then extracted again with DCM (0.5 ml). Combined organics were washed with water (2 X 0.5 mL), dried (Na₂SO₄) and evaporated to dryness. This material was chromatographed on silica, using ethyl acetate / hexanes to give the desired product (12 mg, 50%) as a colorless resin. ¹H NMR (300 MHz, CDCl₃) δ 7.80 (m, 3H), 7.65 – 7.46 (m, 1H), 7.37 (m, 2H), 7.33 – 7.10 (m, 2H), 6.94 (m, 2H), 6.71 (m, 2H), 3.88 (m, 3H), 3.74 (m, 2H), 3.61 – 3.31 (m, 2H), 3.05 (m, 2H), 2.80 (m, 5H), 2.25 (m, 2H), 1.82 (m, 4H), 1.68 – 1.51 (m, 4H), 1.51 – 1.32 (m, 5H), 1.17 – 0.99 (m, 5H), 0.99 – 0.69 (m, 7H), 0.08 (m, 6H). MS calculated for C₄₁H₅₉FN₄O₇SSi [M+H]⁺: 799. Found: 799.



The following examples were prepared using the same method:

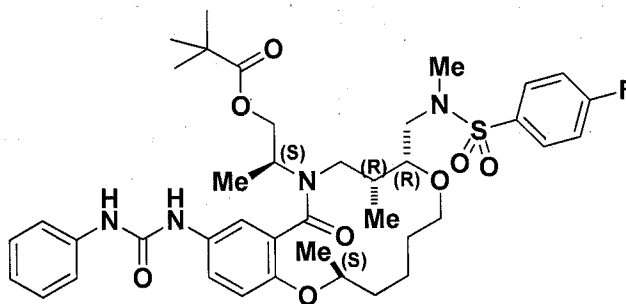
No.	Structure	Name	MS
119		3-[(2S,8R,9R)-11-{2-[(tert-butyl dimethylsilyl)oxy]ethyl}-2,9-dimethyl-8-[[N-methyl(4-fluorobenzene)sulfonamido]methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	[M+H] ⁺ calcd 785; found, 785
120		3-[(2S,8R,9R)-11-[(2R)-1-[(tert-butyl dimethylsilyl)oxy]propan-2-yl]-2,9-dimethyl-8-[[N-methyl(4-fluorobenzene)sulfonamido]methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	[M+H] ⁺ calcd 799; found, 799



- 5 **(S)-2-((2S,8R,9R)-8-((4-fluoro-N-methylphenylsulfonamido)methyl)-2,9-dimethyl-12-oxo-14-(3-phenylureido)-3,4,5,6,9,10-hexahydrobenzo[b][1,9,5]dioxazacyclotetradecin-11(2H,8H,12H)-yl)propyl 4-methylbenzenesulfonate (121)**

To a solution of alcohol **53** (0.0861 g, 0.126 mmol) in dry DCM (2.51 ml) under N₂ atmosphere was added triethylamine (0.070 ml, 0.503 mmol), followed by *p*-toluenesulfonyl chloride (0.048 g, 0.251 mmol), and DMAP (7.68 mg, 0.063 mmol). The resulting mixture was stirred at room temperature for 15h. The reaction was diluted with DCM, washed with water (3 X), dried over Na₂SO₄ and evaporated to dryness. This material was chromatographed on silica, using ethyl acetate / hexanes to afford the title compound (38 mg, 36%). ¹H NMR (300 MHz, CDCl₃) δ 7.81 (m, 3H), 7.51 (d, 2H), 7.40 (d, 2H), 7.34 – 7.09 (m, 5H), 7.05 (m, 1H), 6.83 (m, 3H), 4.57 – 4.43 (m, 1H), 4.43 – 3.98 (m, 2H), 3.86 – 3.70 (m, 1H), 3.63 (m, 1H), 3.39 – 2.97 (m, 4H), 2.81 (m, 3H), 2.15 (s, 3H), 2.01 (m, 2H), 1.76 (m, 1H), 1.65 – 1.37 (m, 6H), 1.26 (m, 8H), 1.08 (d, 2H), 0.98 – 0.78 (m, 1H). MS calculated for C₄₂H₅₁FN₄O₉S₂ [M+H]⁺: 839. Found: 839.

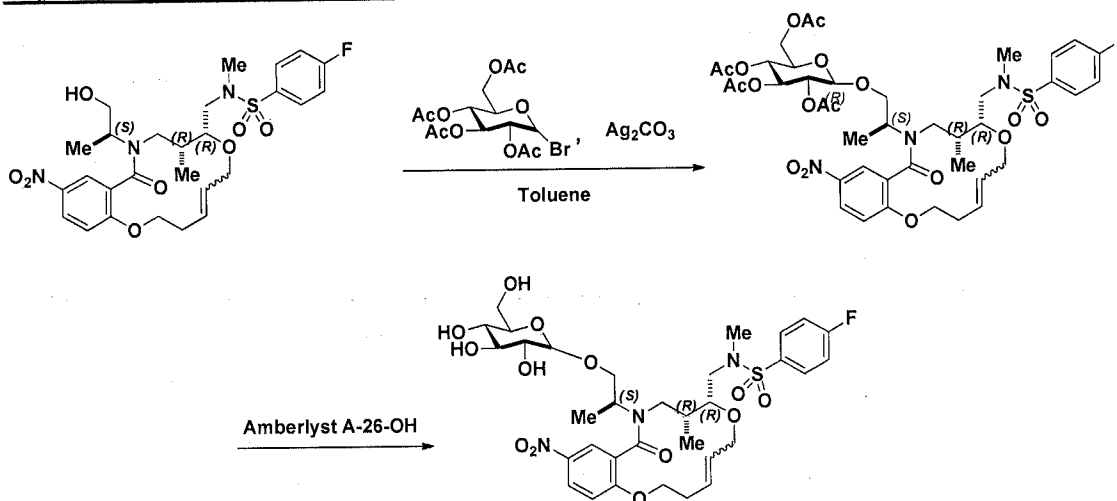
- 151 -

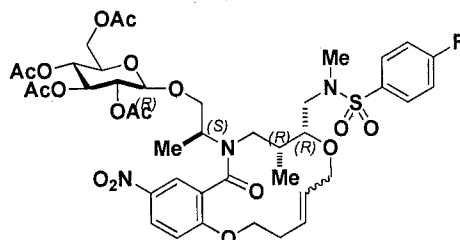


5 (2S)-2-[(2S,8R,9R)-2,9-dimethyl-8-{[N-methyl(4-fluorobenzene)sulfonamido]methyl}-12-oxo-14-[(phenylcarbamoyl)amino]-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-11-yl]propyl 2,2-dimethylpropanoate (122)

To a solution of alcohol **53** (0.041 g, 0.060 mmol) in dry DCM (0.599 ml) was added pyridine (0.024 ml, 0.299 mmol) followed by pivaloyl chloride (17.84 μ l, 0.148 mmol) under N₂ atmosphere. The resulting mixture was stirred at room temperature for 15h. The reaction was diluted with DCM (10 ml) and washed with water (10 ml) and brine. The organic phase was then separated, dried (Na₂SO₄) and evaporated to dryness. This material was chromatographed on silica, using methanol / dichloromethane to afford 30 mg (15%) of the desired product. ¹H NMR (300 MHz, CDCl₃) δ 7.79 (m, 2H), 7.65 – 7.45 (m, 1H), 7.37 (m, 2H), 7.29 – 7.03 (m, 4H), 6.98 (s, 1H), 6.75 (m, 2H), 4.56 (m, 2H), 4.46 – 4.31 (m, 1H), 4.26 – 4.03 (m, 2H), 3.93 (s, 3H), 3.78 – 3.62 (m, 1H), 3.14 (m, 2H), 2.88 (m, 3H), 2.75 (m, 3H), 1.75 (m, 2H), 1.53 (m, 6H), 1.39 – 1.11 (m, 4H), 1.04 (m, 5H), 0.92 – 0.60 (m, 7H). MS calculated for C₄₀H₅₃FN₄O₈S [M+H]⁺: 769. Found: 769.

Glycosylation of free-alcohol

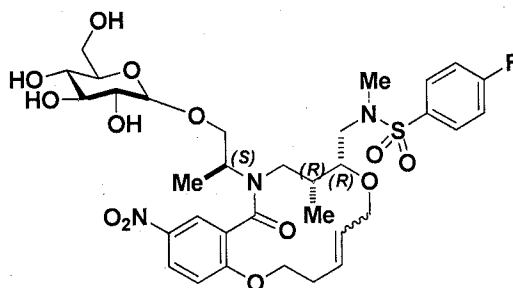




Intermediate AAA:

- 5 **(2R,3S,4S)-2-(acetoxymethyl)-6-(((S)-2-((8R,9R,E)-8-((4-fluoro-N-methylphenylsulfonamido)methyl)-9-methyl-14-nitro-12-oxo-2,3,9,10-tetrahydrobenzo[b][1,9,5]dioxazacyclotetradecin-11(6H,8H,12H)-yl)propoxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate**
- 10 Silver carbonate (186mg, 0.676mmol) was suspended in a solution of 4-fluoro-N-(((8R,9R,E)-11-((S)-1-hydroxypropan-2-yl)-9-methyl-14-nitro-12-oxo-2,3,6,8,9,10,11,12-octahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)-N-methylbenzenesulfonamide (98mg, 0.169mmol) and (2R,3R,4S,5R)-2-(acetoxymethyl)-6-bromotetrahydro-2H-pyran-3,4,5-triyl triacetate (278mg, 0.676)
- 15 in anhydrous toluene (1.127mL) in a sealed vial. The suspension was stirred at heated at 110°C for 72h. The reaction was cooled to rt and an additional to 2 eqv of silver carbonate (93mg, 0.338mmol) was added and the reaction was heated to 110°C and stirred for 48h before being cooled to rt. The insoluble products were filtered off via a celite pad and washed with 20mL DCM and 20mL MeOH and the
- 20 filtrate was concentrated under reduced pressure. The crude product was chromatographed on silica, eluting with 30%-80% ethyl acetate/hexanes to afford 46mg (30% yield of desired) of pure product. ¹H NMR (300 MHz, CDCl₃) δ 8.25 (m, 1H), 8.05 (m, 1H), 7.82 (s, 2H), 7.16 (s, 2H), 6.95 (m, 1H), 5.25 (m, 1H), 5.05 (m, 2H), 4.20 (s, 6H), 3.74 (s, 3H), 2.81 (t, *J* = 21.1, 3H), 2.60 (m, 1H), 2.07 (m, 15H), 1.57 (s, 8H), 1.01 (d, *J* = 7.3, 6H). MS (ESI) calcd for C₄₁H₅₂FN₃O₁₇S [M + H]⁺; 910. Found: 910.

Example 123:



- 30

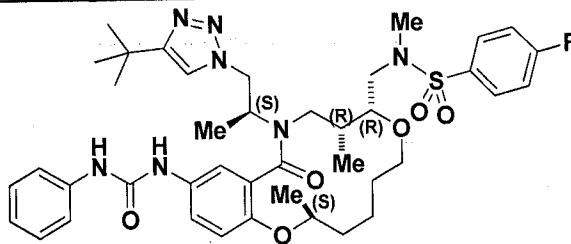
**4-fluoro-N-methyl-N-(((8R,9R,E)-9-methyl-14-nitro-12-oxo-11-((2S)-1-
(((3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-
yl)oxy)propan-2-yl)-2,3,6,8,9,10,11,12-**

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octahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)benzenesulfonamide

(2R,3S,4S)-2-(acetoxymethyl)-6-((S)-2-((8R,9R,E)-8-((4-fluoro-N-methylphenyl)sulfonamido)methyl)-9-methyl-14-nitro-12-oxo-2,3,9,10-tetrahydrobenzo[b][1,9,5]dioxazacyclotetradecin-11(6H,8H,12H)-yl)propoxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate (11mg, 0.012mmol) was dissolved in methanol (0.604mL) and was treated with amberlyst A-26-OH (17mg, 0.019mmol) in a sealed vial. The reaction mixture was shaken for 1h. The reaction mixture was filtered and washed with an excessive amount of MeOH (25mL). The filtrate was concentrated under reduce pressure and chromatographed on silica, eluting with 0-10% methanol/methylene chloride to afford 4mg (45% yield) of pure product. ¹H NMR (300 MHz, CDCl₃) δ 8.11 (d, *J* = 51.7, 2H), 7.80 (s, 2H), 7.17 (s, 2H), 6.99 (s, 1H), 5.58 (m, 2H), 4.26 (m, 4H), 3.87 (s, 3H), 3.63 (m, 4H), 3.37 (m, 3H), 2.91 (d, *J* = 7.3, 1H), 2.74 (s, 2H), 2.61 (s, 1H), 1.67 (s, 5H), 1.19 (d, *J* = 34.1, 6H), 0.86 (d, *J* = 21.0, 6H). MS (ESI) calcd for C₃₃H₄₄FN₃O₁₃S [M + H]⁺: 742. Found: 742.

Triazole formation Example 124:



20

3-[(2S,8R,9R)-11-[(2S)-1-(4-tert-butyl-1H-1,2,3-triazol-1-yl)propan-2-yl]-2,9-dimethyl-8-{[N-methyl(4-fluorobenzene)sulfonamido]methyl}-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea (124)

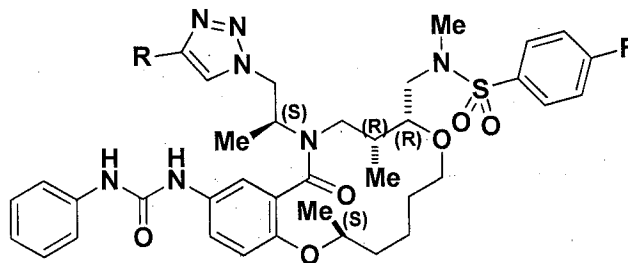
25

To a mixture of azide **89** (0.0165 g, 0.023 mmol) and 3,3-dimethylbut-1-yne (5.72 μl, 0.046 mmol) in dry Toluene (0.465 ml, Density: 0.865 g/ml) was added Tetrakis (acetonitrile) copper (I) hexafluorophosphate (0.026 g, 0.116 mmol) under N₂ atmosphere at room temperature. The resulting solution was heated at 80°C for 1h. The reaction was then cooled to room temperature and concentrated under vacuum. This material was chromatographed on silica, using ethyl acetate / hexanes to afford the final product (4 mg, 19%) as colorless resin. ¹H NMR (300 MHz, CDCl₃) δ 7.72 – 7.60 (m, 2H), 7.54 (m, 2H), 7.43 (s, 1H), 7.33 – 7.21 (m, 2H), 7.21 – 7.04 (m, 5H), 6.63 (m, 1H), 5.36 (m, 1H), 4.49 (s, 1H), 3.84 (s, 1H), 3.61 (m, 2H), 3.38 (m, 3H), 3.05 (s, 1H), 2.89 (s, 1H), 2.80 (s, 3H), 2.62 (s, 2H), 1.75 (s, 1H), 1.65 (s, 4H), 1.52 (m, 5H), 1.31 – 1.00 (m, 9H), 0.98 – 0.82 (m, 2H), 0.76 (m, 4H), 0.12 (m, 2H). MS calculated for C₄₁H₅₄FN₇O₆S [M+H]⁺: 792. Found: 792.

35

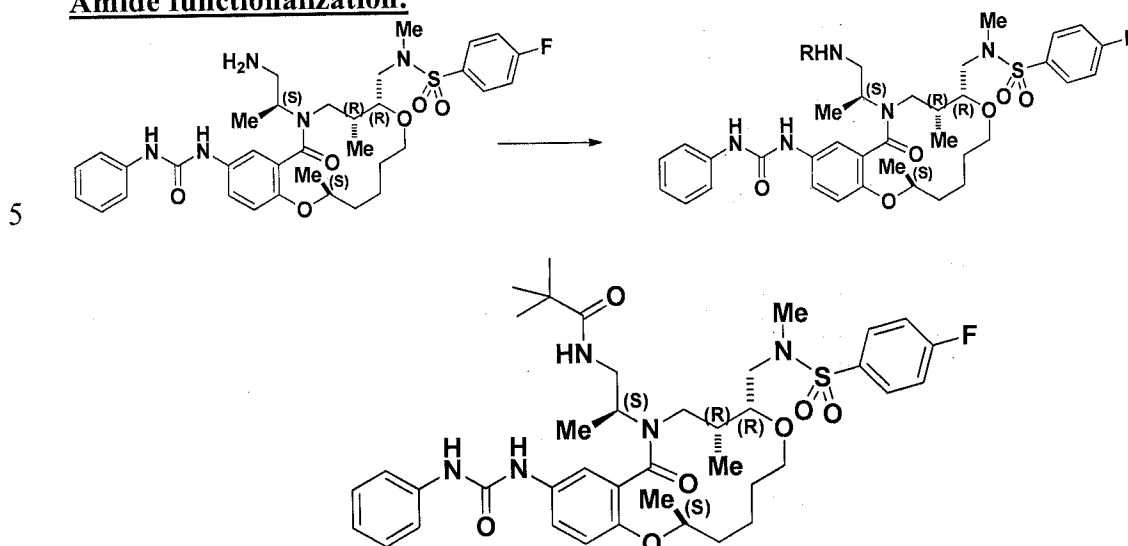
40

The following example was also prepared using the same method:



No.	Structure	Name	MS
125		3-[(2S,8R,9R)-11-[(2S)-1-[4-(methoxymethyl)-1H-1,2,3-triazol-1-yl]propan-2-yl]-2,9-dimethyl-8-[[N-methyl(4-fluorobenzene)sulfonamido]methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	[M+H] ⁺ calcd 780; found, 780
126		3-[(2S,8R,9R)-11-[(2S)-1-(4-cyclopropyl-1H-1,2,3-triazol-1-yl)propan-2-yl]-2,9-dimethyl-8-[[N-methyl(4-fluorobenzene)sulfonamido]methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	[M+H] ⁺ calcd 776; found, 776

Amide functionalization:



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N-((S)-2-((2S,8R,9R)-8-((4-fluoro-N-methylphenylsulfonamido)methyl)-2,9-dimethyl-12-oxo-14-(3-phenylureido)-3,4,5,6,9,10-hexahydrobenzo[b][1,9,5]dioxazacyclotetradecin-11(2H,8H,12H)-yl)propyl)pivalamide (127)

5

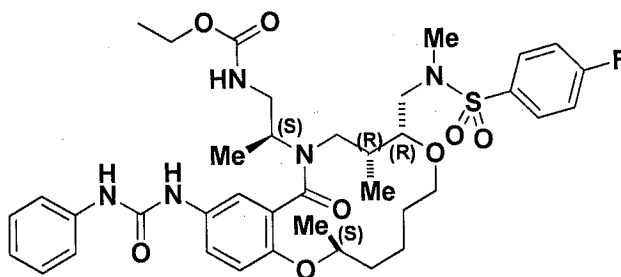
To a solution of amine **94** (38 mg, 0.056 mmol) in DCM (.56 ml) under N₂ was added 2,6-lutidine (1.648 ml, 2.041 mmol) aqueous solution, followed by pivaloyl chloride (10 μ L, 0.084 mmol). The reaction mixture was stirred at room temperature for 16 h then diluted with EtOAc and water. The aqueous phase was separated and washed with EtOAc, then loaded onto a SiO₂ plug and chromatographed on silica, using methanol / dichloromethane to give 15 mg (36%) of the final product as colorless resin. ¹H NMR (300 MHz, CDCl₃) δ 7.78-7.66 (m, 3H), 7.41-7.34 (m, 2H), 7.25 – 7.03 (m, 3H), 6.98 (m, 1H), 6.86 (m, 1H), 6.79-6.67 (m, 1H), 4.64 (m, 1H), 4.05-3.82 (m, 2H), 3.81-3.68 (m, 2H), 3.58-3.47 (m, 1H), 3.18-3.01 (m, 2H), 2.96-2.83 (m, 2H), 2.74 (s, 3H), 2.11-1.95 (m, 1H), 1.87-1.69 (m, 2H), 1.66-1.33 (m, 8H), 1.31-1.22 (m, 1H) 1.20 (s, 9H), 1.18-0.93 (m, 6H), 0.80 (m, 3H). MS calculated for C₄₀H₅₄N₅O₇S : 768 [M+H]⁺. Found 768.

15

The following example was prepared from the same method:

20

No.	Structure	Name	MS
128		N-[(2S)-2-[(2S,8R,9R)-2,9-dimethyl-8-[[N-methyl(4-fluorobenzene)sulfonamido]methyl]-12-oxo-14-[(phenylcarbamoyl)amino]-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-11-yl]propyl]acetamide	[M+H] ⁺ calcd 726; found, 726



ethyl N-[(2S)-2-[(2S,8R,9R)-2,9-dimethyl-8-[[N-methyl(4-fluorobenzene)sulfonamido]methyl]-12-oxo-14-[(phenylcarbamoyl)amino]-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-11-yl]propyl]carbamate (129)

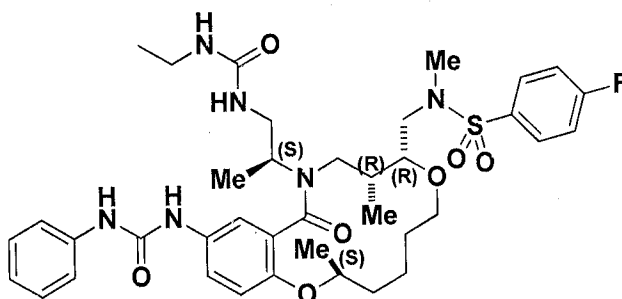
25

To a solution of amine **94** (0.038 g, 0.055 mmol) in dioxane (1.375 ml) was added sodium bicarbonate (0.267 ml, 0.330 mmol) followed by ethyl chloroformate (10.52 μ L, 0.110 mmol) under N₂ atmosphere. The resulting mixture was stirred at room temperature for 15h. The reaction was diluted with water (10 ml) and EtOAc

30

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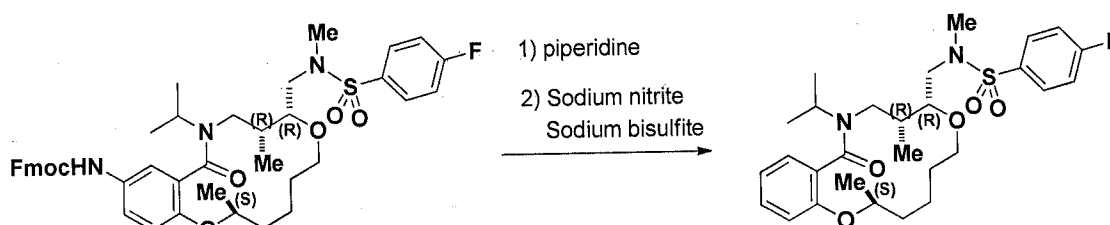
(10 ml) and the product extracted with EtOAc (10 ml). Combined organics were then washed with water and brine, dried (Na_2SO_4) and evaporated to dryness. This material was chromatographed on silica, using methanol / dichloromethane to afford 23 mg (54%) of the desired product as colorless resin. ^1H NMR (300 MHz, CDCl_3) δ 8.51 (s, 1H), 8.18 (s, 1H), 7.78 (m, 3H), 7.57 – 7.32 (m, 2H), 7.32 – 7.10 (m, 3H), 6.93 (s, 2H), 6.87 – 6.66 (m, 1H), 4.63 (s, 1H), 4.10 (s, 2H), 3.86 (s, 2H), 3.67 (s, 1H), 3.10 (s, 2H), 2.91 (m, 4H), 2.75 (s, 2H), 1.62 (s, 6H), 1.47 – 1.35 (m, 3H), 1.32 (s, 2H), 1.18 (m, 7H), 1.06 – 0.90 (m, 3H), 0.80 (m, 2H). MS calculated for $\text{C}_{38}\text{H}_{50}\text{FN}_5\text{O}_8\text{S}$ $[\text{M}+\text{H}]^+$: 756. Found: 756.



3-[(2S,8R,9R)-11-[(2S)-1-[(ethylcarbamoyl)amino]propan-2-yl]-2,9-dimethyl-8-{[N-methyl(4-fluorobenzene)sulfonamido]methyl}-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea (130)

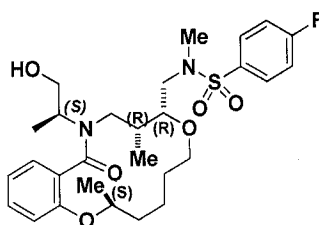
To a solution of amine **94** (0.038 g, 0.055 mmol) in dry DCM (0.550 ml) was added isocyanatoethane (0.013 ml, 0.165 mmol) under N_2 atmosphere. The resulting mixture was stirred at room temperature for 15h. The reaction was diluted with DCM (10 ml), the organic phase separated, washed with water (2 X 10 ml), dried (Na_2SO_4) and evaporated to dryness. This material was chromatographed on silica, using methanol / dichloromethane to give the final product (3 mg, 6%) as colorless resin. ^1H NMR (300 MHz, CDCl_3) δ 8.15 (m, 1H), 7.87 – 7.76 (m, 1H), 7.76 – 7.66 (m, 1H), 7.66 – 7.49 (m, 1H), 7.42 (s, 1H), 7.26 (s, 5H), 7.07 – 6.90 (m, 1H), 6.56 – 6.43 (m, 1H), 4.21 (s, 1H), 3.68 – 3.51 (m, 1H), 2.92 (s, 2H), 2.74 – 2.54 (m, 3H), 2.32 – 2.11 (m, 3H), 2.00 (s, 3H), 1.55 (m, 6H), 1.44 – 1.02 (m, 6H), 0.87 (m, 9H), 0.61 (s, 2H), 0.07 (s, 3H). MS calculated for $\text{C}_{38}\text{H}_{51}\text{FN}_6\text{O}_7\text{S}$ $[\text{M}+\text{H}]^+$: 755. Found: 755.

Deamination of anilines to yield Examples 131-132:



4-fluoro-N-(((2S,8R,9R)-11-isopropyl-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)-N-methylbenzenesulfonamide (131)

- 5 To a solution of N-(((2S,8R,9R)-14-amino-11-isopropyl-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)-4-fluoro-N-methylbenzenesulfonamide (75 mg, 0.097 mmol) in DMF (972 μ l) under N₂ was added piperidine (14.43 μ l, 0.146 mmol). The reaction was stirred for 1h then quenched with water (1 mL) and extracted with EtOAc (2 x 5
- 10 mL). The combined organic layers were dried with sodium sulfate, concentrated and dried. The crude taken to the next step. To a solution of the crude amine N-(((2S,8R,9R)-14-amino-11-isopropyl-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)-4-fluoro-N-methylbenzenesulfonamide (20 mg, 0.036 mmol) in EtOH (1.6 ml) and Acetic Acid
- 15 (0.3 ml) was added under N₂ and Sodium nitrite (455 μ l, 0.364 mmol) in 0.45 mL water and then Sodium bisulfite (25mg, 0.364 mmol) in 0.6 mL water was added. The solution turned orange upon addition of NaNO₂. The reaction was stirred for 16 h and the reaction mixture was extracted with DCM and the organic phase washed with water, dried over sodium sulfate and evaporated under reduced
- 20 pressure. The reaction was purified by column chromatography using DCM/Methanol to afford the desired product (12.4 mg, 64%). ¹H NMR (500 MHz, CDCl₃) δ 7.88–7.57 (m, 2H), 7.19 (s, 2H), 7.14–6.94 (m, 2H), 6.90–6.66 (m, 2H), 4.64–4.29 (m, 1H), 4.21–3.96 (m, 1H), 3.97–3.79 (m, 1H), 3.76–3.51 (m, 2H), 3.52–3.30 (m, 1H), 2.79 (s, 2H), 2.70–2.41 (m, 3H), 2.31–2.01 (m, 3H), 1.98 (s, 2H), 1.51
- 25 (s, 4H), 1.19 (s, 7H), 0.92 (s, 6H). MS (ESI) calcd for C₂₈H₃₉FN₂O₅S [M + H]⁺: 535. Found: 535.



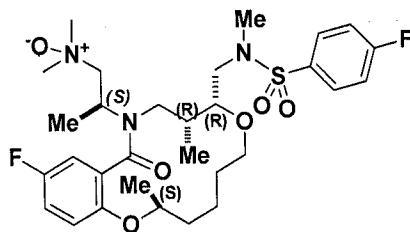
- 30 **4-fluoro-N-(((2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl)methyl)-N-methylbenzene-1-sulfonamide (132)**

- This product was prepared with the same procedure as for the preparation of 4-fluoro-N-(((2S,8R,9R)-11-isopropyl-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)-N-methylbenzenesulfonamide. During this deamination, the TBS group was removed, yielding the free hydroxyl compound as the final product. ¹H NMR (300 MHz, CDCl₃) δ 7.86–7.69 (m, 2H), 7.38–7.29 (m, 1H), 7.24–7.08 (m, 3H), 7.04–6.79 (m,
- 35 2H), 5.11–5.01 (m, 1H), 4.83–4.70 (m, 1H), 4.60–4.46 (m, 1H), 4.05 (m, 1H), 3.98–3.82 (m, 2H), 3.81–3.70 (m, 1H), 3.67–3.42 (m, 4H), 3.19–2.91 (m, 2H), 2.90–2.85
- 40 (m, 3H), 2.76–2.58 (m, 2H), 2.40 (m, 1H), 1.95–1.75 (m, 2H), 1.73–1.49 (m, 2H),

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1.47-1.30 (m, 5H), 1.10 – 0.72 (m, 6H). MS calculated for $C_{28}H_{39}N_2O_6S$ $[M+H]^+$: 551. Found: 551.

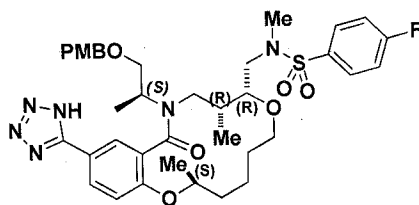
N-Oxide formation



(S)-2-((2S,8R,9R)-14-fluoro-8-((4-fluoro-N-methylphenylsulfonamido)methyl)-2,9-dimethyl-12-oxo-3,4,5,6,9,10-hexahydrobenzo[b][1,9,5]dioxazacyclotetradecin-11(2H,8H,12H)-yl)-N,N-dimethylpropan-1-amine oxide (133)

N-(((2S,8R,9R)-11-((S)-1-(dimethylamino)propan-2-yl)-14-fluoro-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)-4-fluoro-N-methylbenzenesulfonamide (16 mg, 0.027 mmol) was dissolved in DCM (269 μ l) and to this was added mCPBA (660 mg, 2.9 mmol). The mixture was stirred at room temperature for 2 h and after this time the solvent was evaporated under reduced pressure to afford a crude material. This material was purified by column chromatography using MeOH/DCM to afford the desired product (10 mg, 62%). δ 7.83–7.55 (m, 2H), 7.20–7.08 (m, 2H), 7.02–6.93 (m, 1H), 6.94–6.82 (m, 1H), 6.81–6.61 (m, 1H), 4.69–4.51 (m, 1H), 4.16–3.71 (m, 4H), 3.52–3.28 (m, 3H), 3.24–2.88 (m, 4H), 2.86–2.60 (m, 4H), 2.13–1.89 (m, 2H), 1.84–1.64 (m, 2H), 1.66–1.29 (m, 7H), 1.28–0.85 (m, 6H), 0.82–0.55 (m, 3H). MS (ESI) calcd for $C_{30}H_{43}F_2N_3O_6S$ $[M + H]^+$: 612. Found: 612.

Tetrazole formation:

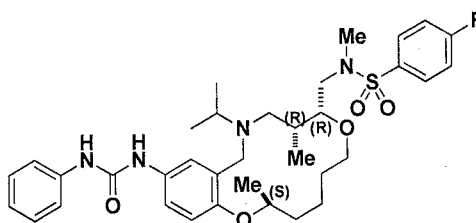


4-fluoro-N-(((2S,8R,9R)-11-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2,9-dimethyl-12-oxo-14-(1H-tetrazol-5-yl)-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)-N-methylbenzenesulfonamide (134)

A 5 mL microwave vial containing nitrile N-(((2S,8R,9R)-14-cyano-11-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)-4-fluoro-N-methylbenzenesulfonamide (21 mg, .03 mmol), sodium azide (11.77 mg, 0.181

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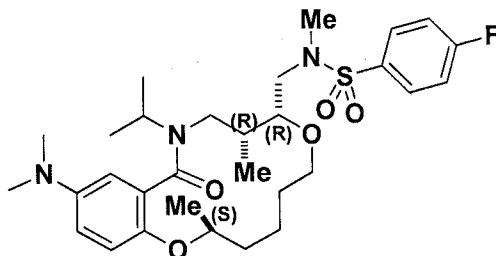
mmol), zinc bromide (6.58 mg, 0.045 mmol), 700 μ L of water and 700 μ L of 2-propanol was heated in with a Biotage Initiator 2.5 Microwave Synthesizer microwave reactor at 150 $^{\circ}$ C for a total of 210 minutes. The mixture was evaporated under reduced pressure and purified by column chromatography using ethylacetate/hexane to afford the desired compound (15 mg, 67%). 1 HNMR (300 MHz, CDCl_3) δ 8.03–7.86 (m, 2H), 7.86–7.55 (m, 2H), 7.25–7.00 (m, 4H), 6.94–6.77 (m, 2H), 6.77–6.61 (m, 1H), 4.66–4.33 (m, 2H), 4.17–3.97 (m, 2H), 3.94–3.70 (m, 3H), 3.66–3.50 (m, 2H), 3.48–3.32 (m, 2H), 3.25–3.00 (m, 2H), 2.94–2.67 (m, 4H), 2.47–2.17 (m, 3H), 2.21–1.89 (m, 3H), 1.84–1.29 (m, 6H), 1.26–1.14 (m, 2H), 1.14–0.71 (m, 5H). MS (ESI) calcd for $\text{C}_{37}\text{H}_{47}\text{FN}_6\text{O}_7\text{S}$ $[\text{M} + \text{H}]^+$: 739. Found: 739.

Amide reduction:

3-[(2S,8R,9R)-2,9-dimethyl-8-{[N-methyl(4-fluorobenzene)sulfonamido]methyl}-11-(propan-2-yl)-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxacyclotetradecin-14-yl]-1-phenylurea (135)
To a chilled (ice- H_2O bath) solution of 4-fluoro-N-(((2S,8R,9R)-11-isopropyl-2,9-dimethyl-12-oxo-14-(3-phenylureido)-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)-N-methylbenzenesulfonamide in dry THF (500 μ L) under nitrogen was added dropwise over 5 min borane-methyl sulfide complex (9.93 μ L, 0.105 mmol). Let warm to rt, then added a reflux condenser and heated in to 70 $^{\circ}$ C in an oil bath. After 4 h the reaction was cooled to roomtemperature, then chilled in an ice- H_2O bath and added MeOH slowly dropwise until the bubbling slowed. More of MeOH was added and the reaction stirred at rt until no bubbling seen. The solvent was removed in vacuo, and the crude oil was coevaporated with MeOH. MeOH (2 ml) was added to the crude mixture followed by Na/K tartrate (2 ml, 10%) and the reaction mixture was heated at 80 $^{\circ}$ C (oil bath temp) for 16 hours. The reaction was cooled and concentrated to remove MeOH and extracted into EtOAc. Washed organics with brine, dried (Na_2SO_4) and solvent evaporated. Purification with flash chromatography followed (MeOH/DCM) afforded the desired product (2.41mg, 18%).
MS (ESI) calcd for $\text{C}_{35}\text{H}_{47}\text{FN}_4\text{O}_5\text{S}$ $[\text{M} + \text{H}]^+$: 655. Found: 655.

Reductive methylation:

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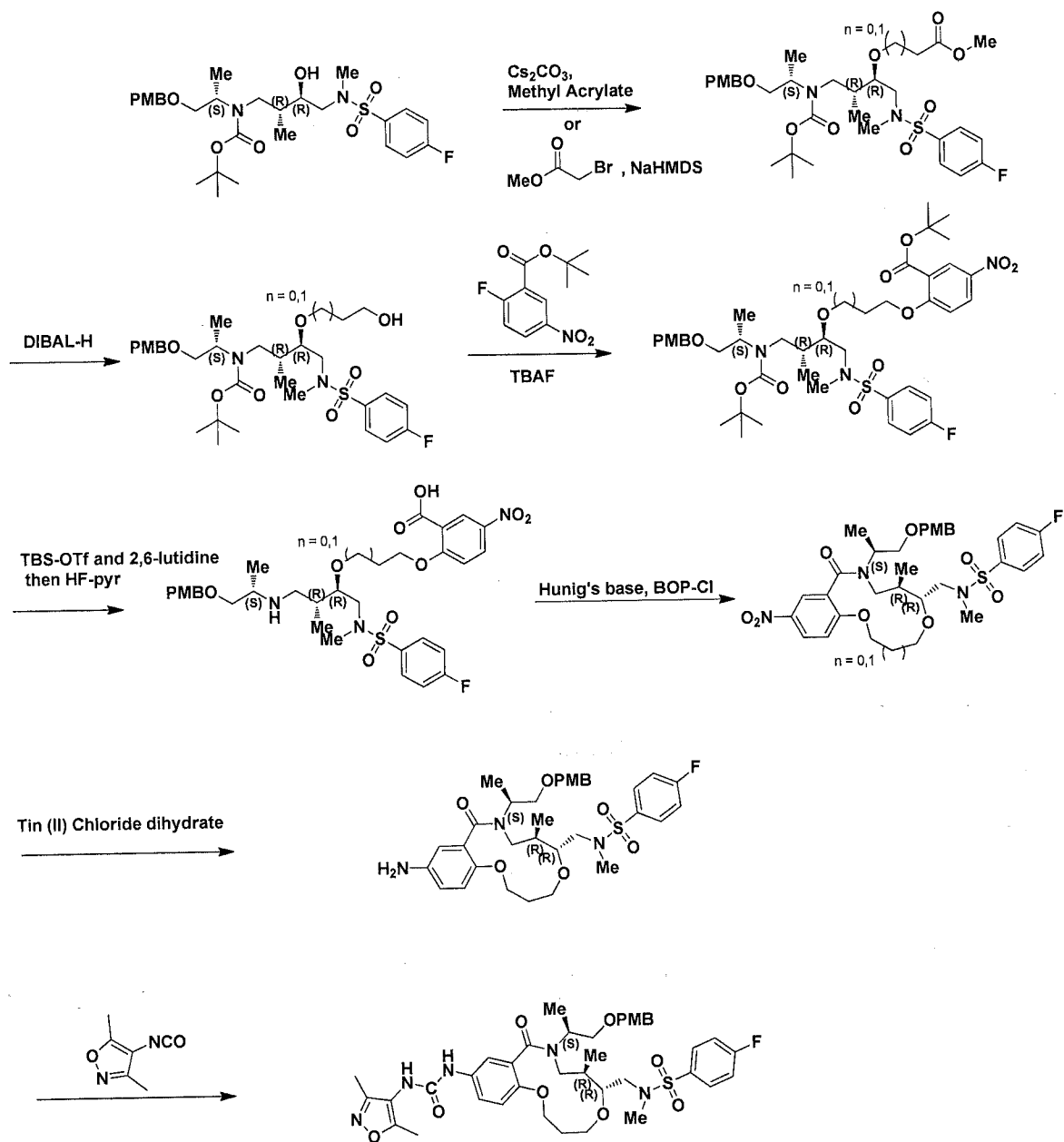
N-(((2S,8R,9R)-14-(dimethylamino)-11-isopropyl-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)-4-fluoro-N-methylbenzenesulfonamide (136)

N-(((2S,8R,9R)-14-amino-11-isopropyl-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)-4-fluoro-N-methylbenzenesulfonamide was dissolved in THF:MeOH:AcOH (4:1:0.2) (364 μ l) and formaldehyde (54.2 μ l, 0.728 mmol) was added. Stirred at rt for 1 hr then sodium cyanoborohydride (22.86 mg, 0.364 mmol) was added. The reaction was stirred for 16h and then quenched with saturated sodium bicarbonate solution (2 ml), extracted with ethyl acetate and solvent evaporated. Purification with flash chromatography followed (MeOH/DCM) afforded the desired product (17 mg, 81%).

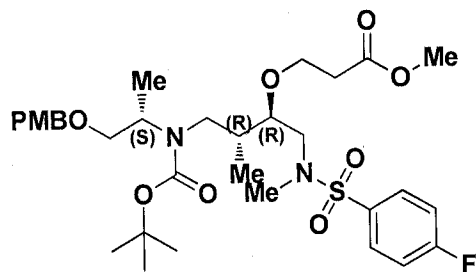
^1H NMR (300 MHz, CDCl_3) δ 7.85–7.58 (m, 2H), 7.14–6.92 (m, 3H), 6.90–6.42 (m, 2H), 4.57–4.14 (m, 2H), 4.02–3.64 (m, 3H), 3.62–3.32 (m, 2H), 3.29–2.88 (m, 1H), 2.86–2.60 (m, 5H), 2.59–2.41 (m, 4H), 2.30–1.84 (m, 3H), 1.84–1.36 (m, 4H), 1.37–1.00 (m, 8H), 1.00–0.61 (m, 5H). MS (ESI) calcd for $\text{C}_{30}\text{H}_{44}\text{FN}_3\text{O}_5\text{S}$ $[\text{M} + \text{H}]^+$: 578. Found: 578.

General synthetic scheme for the preparation of the 12-membered ring analogue.

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Intermediate BBB1:

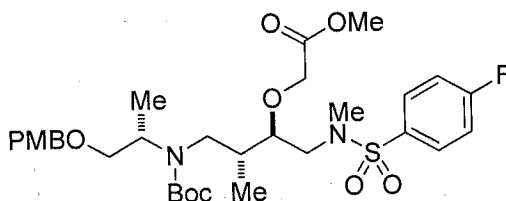


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Synthesis of methyl 3-(((2R,3R)-4-((tert-butoxycarbonyl)((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)amino)-1-(4-fluoro-N-methylphenylsulfonamido)-3-methylbutan-2-yl)oxy)propanoate.

- 5 To a solution of Intermediate **M** (1.17 g, 2.057 mmol) in Tert-Butanol (0.1 M) under N₂ was added methyl acrylate (7.46 ml, 82 mmol) and cesium carbonate (0.670 g, 2.057 mmol). The reaction was stirred at room temperature for 48 hours. The reaction was then diluted with a saturated ammonium chloride solution and extracted into ethyl acetate. The organic layers were washed with H₂O, brine, dried
 10 over Na₂SO₄ and solvent evaporated. The residue was purified by silica gel chromatography using ethyl acetate/hexanes to afford the desired product (1.20g, 89% yield). ¹H NMR (300 MHz, CDCl₃) δ 7.72 (d, 2H), 7.25 – 7.01 (m, 4H), 6.79 (d, 2H), 4.37 (s, 2H), 3.72 (s, 3H), 3.79 – 3.47 (m, 4H), 3.55 (s, 3H), 3.47 – 3.22 (m, 2H), 3.20 – 2.84 (m, 3H), 2.73 (s, 3H), 2.44 (t, 2H), 2.12 – 1.90 (m, 1H), 1.35 (s,
 15 9H), 1.24 – 1.01 (m, 4H), 0.81 (d, 3H). MS (ESI) calcd for C₃₂H₄₇FN₂O₉S [M + H]⁺: 655. Found: 655.

Intermediate BBB2 :



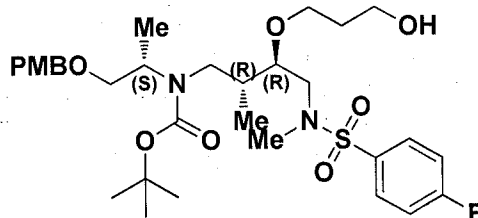
20

Synthesis of Methyl 2-(((2R,3R)-4-((tert-butoxycarbonyl)((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)amino)-1-(4-fluoro-N-methylphenylsulfonamido)-3-methylbutan-2-yl)oxy)acetate

- 25 To a chilled (-78 °C) solution of *tert*-butyl ((2R,3R)-4-(4-fluoro-N-methylphenylsulfonamido)-3-hydroxy-2-methylbutyl)((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)carbamate (**M**) (1.10 g, 1.93 mmol) in dry THF (8.3 mL) and dry DMF (1.4 mL) under N₂ was added methyl 2-bromoacetate (1.8 mL, 19 mmol) followed by sodium *bis*-(trimethylsilyl)amide (5.8 mL, 5.8 mmol).
 30 The solution was stirred 15 min at -78 °C, then the reaction flask was warmed to 3 °C and stirred at this temperature for 16 h. The reaction mixture was then quenched with sat. aq. NH₄Cl, diluted with H₂O and EtOAc, the phases were partitioned and the aqueous was washed with EtOAc, then the organics were washed with H₂O then brine, dried (Na₂SO₄) and the solvent evaporated. Purification was accomplished
 35 with SiO₂ chromatography to yield 0.44 g (36%) of pure product. ¹H NMR (300 MHz, CDCl₃) δ 7.86-7.69 (m, 2H), 7.25 – 7.11 (m, 4H), 6.86 (d, *J* = 8.4 Hz, 2H), 4.47 – 4.39 (m, 2H), 4.13 (s, 2H), 3.93 – 3.64 (m, 3H), 3.78 (s, 3H), 3.71 (s, 3H), 3.60 – 3.37 (m, 2H), 3.28 – 3.06 (m, 3H), 2.84 (s, 3H), 2.26-2.02 (m, 1H), 1.43 (s, 9H), 1.21 (d, *J* = 6.9 Hz, 3H), 0.91 (d, *J* = 6.9 Hz, 3H). MS calculated for
 40 C₃₁H₄₅FN₂O₉SNa [M+Na]⁺: 663. Found: 663.

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Intermediate CCC:



- 5 Synthesis of tert-butyl ((2R,3R)-4-(4-fluoro-N-methylphenylsulfonamido)-3-(3-hydroxypropoxy)-2-methylbutyl)((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)carbamate (CCC1)

BBB1 (0.406 g, 0.620 mmol) was dissolved in Toluene (12.81 ml,) and cooled to -78 °C. DIBAL in Toluene (1.240 ml, 1.240 mmol) was added dropwise to the
 10 reaction mixture. The reaction was let stir for 30 min before removing from the bath and stirring at room temperature. After 2 hours the reaction was complete and it was quenched with methanol (15.37 ml) slowly until there was no more bubbling. Then an additional 15.37 ml of methanol and 6 mL of Rochelle salts were added and the reaction was left to stir overnight. The crude mixture was concentrated under
 15 pressure, water was added and the crude product was extracted with ethyl acetate 3 times. The combined organics were dried over Na₂SO₄ and the product was purified by silica gel chromatography using methanol/DCM to give 268mg of the desired product (69% yield). ¹H NMR (300 MHz, CDCl₃) δ 7.72 (s, 2H), 7.24 – 7.04 (m, 4H), 6.80 (d, 2H), 4.36 (m, 2H), 3.72 (s, 3H), 3.80 – 3.45 (m, 6H), 3.44 – 3.25 (m, 2H), 3.14 – 2.92 (m, 3H), 2.73 (s, 3H), 2.02 – 1.93 (m, 1H), 1.78 – 1.61 (m, 2H),
 20 1.35 (s, 9H), 1.27 – 0.98 (m, 5H), 0.83 (d, 3H). MS (ESI) calcd for C₃₁H₄₇FN₂O₈S [M + H]⁺: 627. Found: 627.

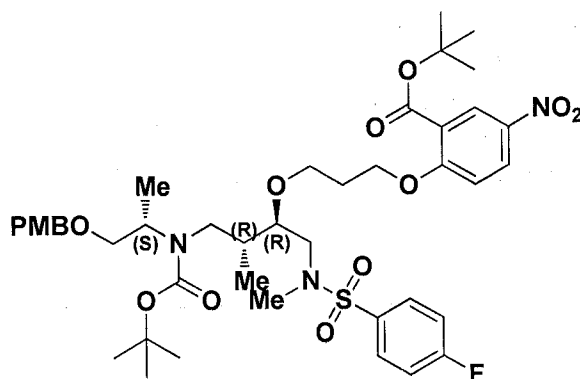
The 11-membered ring analogue was prepared using this method:

25

No.	Structure	Name	MS
CCC2		tert-butyl ((2R,3R)-4-(4-fluoro-N-methylphenylsulfonamido)-3-(2-hydroxyethoxy)-2-methylbutyl)((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)carbamate	[M+H] ⁺ calcd 613; found, 613

Intermediate DDD:

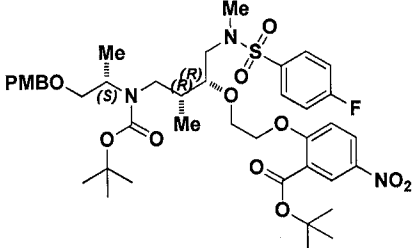
- 164 -

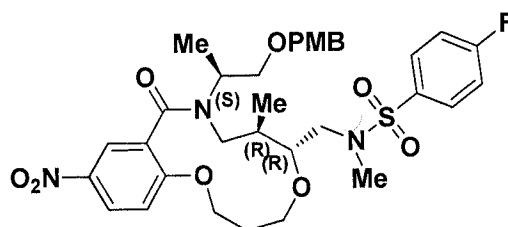


Synthesis of tert-butyl 2-(3-(((2R,3R)-4-((tert-butoxycarbonyl)((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)amino)-1-(4-fluoro-N-methylphenylsulfonamido)-3-methylbutan-2-yl)oxy)propoxy)-5-nitrobenzoate(DDD1)

4A molecular sieves were activated before use by flame-drying under vacuum. To a suspension of 400 mg 4A activated molecular sieves in dry THF (Ratio: 1.000, 0.577 ml) under N₂ was added TBAF (0.692 ml, 0.692mmol) and the suspension was stirred 10 min. Then, a solution of CCC1 (0.217g, 0.346mmol) and tert-butyl 2-fluoro-5-nitrobenzoate (0.125g, 0.519 mmol) in THF (1.154 ml) was added and the mixture was stirred overnight. After 24 hours the reaction was still not complete as monitored by LCMS so 2 other equivalents of TBAF(0.692ml, 0.692 mmol) previously stirred in activated sieves were added and the reaction was complete after further 16 hours. The reaction mixture was quenched with saturated NH₄Cl solution, diluted with ethyl acetate and filtered. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were washed with an acid acetic solution at pH4, brine, dried over Na₂SO₄ and the solvent was evaporated under pressure. The crude product was purified with silica gel chromatography to give 203.5mg of pure product (69% yield). ¹H NMR (300 MHz, CDCl₃) δ 8.40 (d, 1H), 8.13 (d, 1H), 7.73 – 7.50 (m, 2H), 7.18 – 6.80 (m, 5H), 6.71 (d, 8.4, 2H), 4.26 (s, 2H), 3.63 (s, 3H), 3.59 – 3.37 (s, 4H), 3.37 – 3.16 (m, 3H), 3.16 – 2.88 (m, 3H), 2.88 – 2.74 (m, 2H), 2.58 (s, 3H), 1.94 (m, 3H), 1.43 (s, 9H), 1.25 (s, 9H), 1.16 – 0.97 (m, 3H), 0.74 (d, 3H).MS (ESI) calcd for C₄₂H₅₈FN₃O₁₂S [M + H]⁺: 848. Found: 848.

The 11-membered ring analogue was prepared using this method:

No.	Structure	Name	MS
DDD2		tert-butyl 2-(2-(((2R,3R)-4-((tert-butoxycarbonyl)((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)amino)-1-(4-fluoro-N-methylphenylsulfonamido)-3-methylbutan-2-yl)oxy)ethoxy)-5-nitrobenzoate	[M+H] ⁺ calcd 834; found, 834

Intermediate EEE:

Synthesis of 2-(3-(((2R,3R)-1-(4-fluoro-N-methylphenylsulfonamido)-4-(((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)amino)-3-methylbutan-2-yl)oxy)propoxy)-5-nitrobenzoic acid (EEE1)

A solution of DDD1 (0.203 g, 0.239 mmol) in dry DCM (4.79 ml) under N₂ was chilled in a ice-H₂O bath and to this was added 2,6-dimethylpyridine (0.069 ml, 0.598 mmol) followed by tert-butyldimethylsilyl trifluoromethanesulfonate (0.283 ml, 1.197 mmol). The reaction was stirred at 0 °C for 25 min, and the bath was then removed and the reaction was stirred at room temperature for 3h. To the solution was then added 2,6-lutidine (0.069 mL, 0.598 mmol) and the reaction was quenched with saturated NaHCO₃ solution. The layers were separated, and the aqueous layer was extracted with DCM. The combined organic extracts were dried over Na₂SO₄, filtered and concentrated under pressure. The crude residue was dissolved in THF (4.8 mL), transferred to a teflon bottle, and pyridine hydrofluoride (29.8 μL, 0.240 mmol) was added. The reaction was stirred for 1h30. Then the reaction was quenched with a saturated NaHCO₃ solution (bubbling), and diluted with ethyl acetate. The aqueous layer was washed with ethyl acetate, and the organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated to yield the crude product which was carried onto the next step. The crude residue was diluted in dry DCM (8.00 ml) and BOP-Cl (0.122 g, 0.480 mmol) was added at 0 °C. Then Hunig'sBase (0.151 ml, 0.864 mmol) was added and the reaction mixture was slowly warmed to room temperature. After 3 hours the reaction was complete and the solvent was evaporated. The crude mixture was purified by silica gel chromatography using ethyl acetate/hexanes to give 0.144 mg of desired product (89% yield). ¹H NMR (300 MHz, CDCl₃) δ 8.36 – 7.87 (m, 2H), 7.86 – 7.59 (m, 2H), 7.37 – 6.96 (m, 4H), 6.96 – 6.68 (m, 3H), 4.36 (s, 2H), 4.30 – 4.08 (m, 1H), 4.06 – 3.80 (m, 2H), 3.76 – 3.74 (m, 3H), 3.76 – 3.63 (m, 1H), 3.59 – 3.49 (m, 2H), 3.27 – 3.05 (m, 2H), 3.04 – 2.81 (m, 2H), 2.80 – 2.74 (m, 3H), 2.73 – 2.37 (m, 2H),

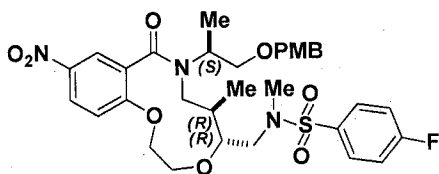
- 166 -

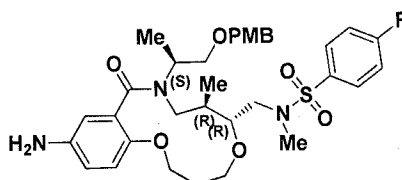
2.23 – 1.68 (m, 2H), 1.65 – 1.50 (m, 1H), 1.26 – 1.00 (m, 3H), 0.88 – 0.69 (m, 3H).

MS (ESI) calcd for C₃₃H₄₀FN₃O₉S [M + H]⁺: 674. Found: 674

The 11-membered ring analogue was prepared using this method:

5

No.	Structure	Name	MS
EEE2		4-fluoro-N-(((5R,6R)-8-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-6-methyl-11-nitro-9-oxo-3,5,6,7,8,9-hexahydro-2H-benzo[e][1,4,8]dioxazacyclo undecin-5-yl)methyl)-N-methylbenzenesulfonamide	[M+H] ⁺ calcd 660; found, 660

Nitro-group reduction:

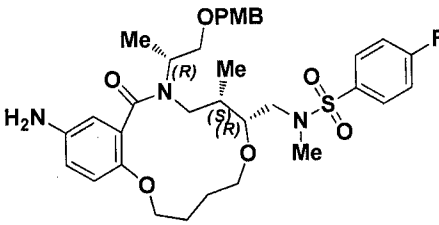
10 **N-(((6R,7R)-12-amino-9-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-7-methyl-10-oxo-2,3,4,6,7,8,9,10-octahydrobenzo[f][1,5,9]dioxazacyclododecin-6-yl)methyl)-4-fluoro-N-methylbenzenesulfonamide(FFF1)**

To a solution of **EEE1** (0.0146 g, 0.022 mmol) in methanol (0.217 ml) was added Tin (II) chloride dihydrate (0.024 g, 0.108 mmol) and the mixture was stirred at 50 °C. After 20 hours the reaction was complete and the methanol was removed under pressure. The product was extracted with ethyl acetate and water was added to dissolve the thick precipitate formed. The layers were separated and the aqueous layer extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over Na₂SO₄ and concentrated. Purification using silica gel chromatography permits to afford 10 mg of pure product (71% yield). ¹H NMR (300 MHz, CDCl₃) δ 8.01 - 7.58 (m, 2H), 7.36 – 6.92 (m, 6H), 6.91 – 6.49 (m, 3H), 4.51 – 4.32 (m, 2H), 4.32 – 4.11(m, 2H), 4.11 – 3.87 (m, 1H), 3.80 - 3.74 (m, 1H), 3.74 – 3.64 (m, 3H), 3.59 – 3.43 (m, 2H), 3.43 – 3.17 (m, 3H), 3.16 – 3.03 (m, 1H), 3.01 – 2.84 (m, 1H), 2.88 – 2.67 (m, 3H), 2.74 – 2.37 (m, 2H), 2.14 – 1.88 (m, 1H), 1.88 – 1.59 (m, 2H), 1.52 – 1.22 (m, 1H), 1.22 – 0.92 (m, 3H), 0.92 – 0.58 (m, 3H).

20 MS (ESI) calcd for C₃₃H₄₂FN₃O₇S [M + H]⁺: 644. Found: 644.

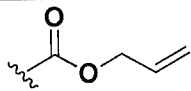
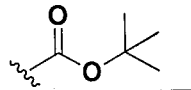
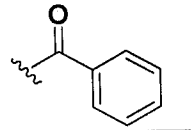
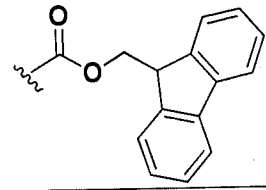
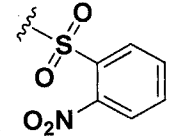
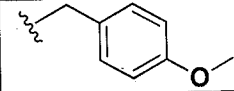
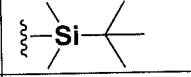
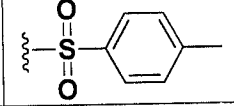
25 The 11 and the 13-membered ring analogues were prepared using this method:

- 167 -

No.	Structure	Name	MS
FFF2		N-(((7R,8S)-13-amino-10-((R)-1-((4-methoxybenzyl)oxy)propan-2-yl)-8-methyl-11-oxo-3,4,5,7,8,9,10,11-octahydro-2H-benzo[b][1,9,5]dioxazacyclotridecin-7-yl)methyl)-4-fluoro-N-methylbenzenesulfonamide	[M+H] ⁺ calcd 658; found, 658

*Intermediate FFF2 was prepared from Intermediate AA20

Abbreviations for protecting groups

Abbreviation	Structure
Alloc	
Boc	
Bz	
Fmoc	
Ns	
PMB	
TBS	
Ts	
CN	

5

General Information

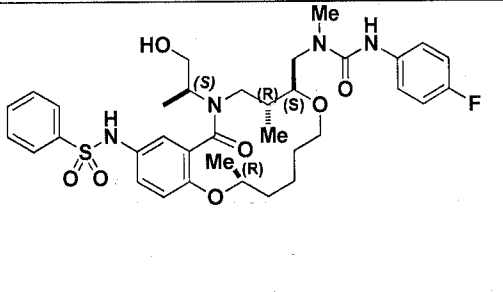
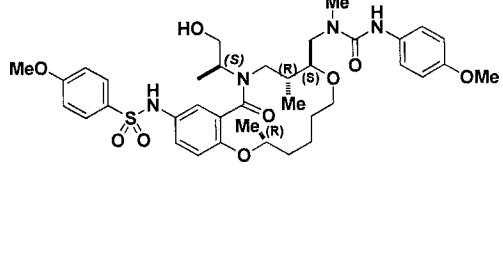
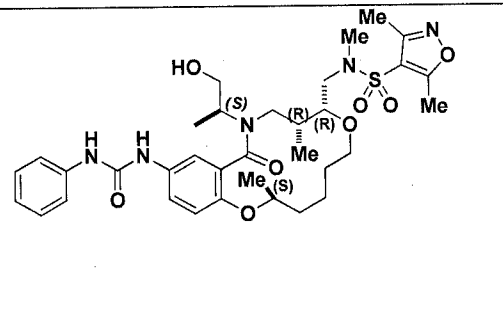
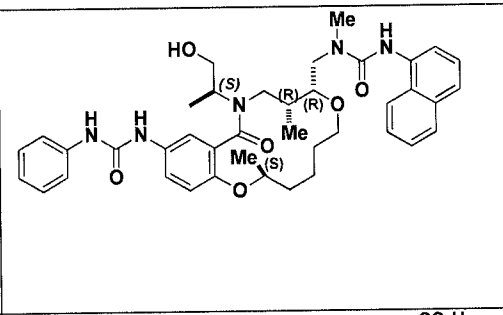
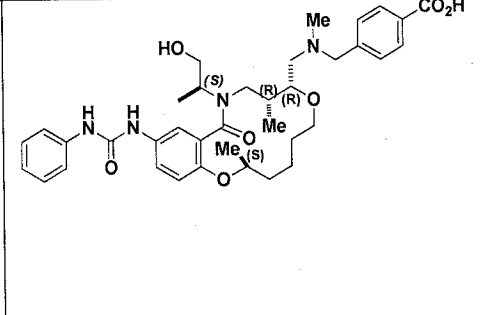
All oxygen and/or moisture sensitive reactions were carried out under N₂

atmosphere in glassware that had been flame-dried under vacuum (~0.5 mmHg) and purged with N₂ prior to use. All reagents and solvents were purchased from commercial vendors and used as received, or synthesized according to the footnoted references. NMR spectra were recorded on a Bruker 300 (300 MHz ¹H, 75 MHz ¹³C) spectrometer. Proton chemical shifts are reported in ppm (δ) referenced to the NMR solvent.¹ Data are reported as follows: chemical shifts, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet; coupling constant(s) in Hz; integration). Unless otherwise indicated NMR data were collected at 25 °C. Flash chromatography was performed using 40-60 μm Silica Gel (60 Å mesh) on a Teledyne Isco Combiflash R_f. Compound purity and identity were determined by LC-MS with two different methods, and by UPLC. Purity was measured by UV absorbance at 210 nm. LCMS method 1:(Alliance 2795, Waters, Milford, MA) Identity was determined on a SQ mass spectrometer by positive and negative electrospray ionization. Mobile phase A consisted of either 0.01% ammonium hydroxide or 0.01% formic acid in water, while mobile phase B consisted of the same additives in acetonitrile. The gradient ran from 5% to 95% mobile phase B over 1.6 minutes at 3 mL/min. An XBridge C18, 3.5 μm, 4.6x30 mm column was used with column temperature maintained at 40 °C. 5 μL of sample solution were injected. LCMS method 2: Identity was determined on an SQ mass spectrometer by positive and negative electrospray ionization. Mobile phase A consisted of 0.01% formic acid in water or pure water, while mobile phase B consisted of 0.01% formic acid in acetonitrile or pure acetonitrile. The gradient ran from 5% to 95% mobile phase B over 1.75 minutes at 1.75 mL/min. An Agilent Poroshell 120 EC-C18, 2.7 μm, 3.0x30 mm column was used with column temperature maintained at 40 °C. 2.1 μL of sample solution were injected. UPLC-MS (Waters, Milford, MA) method: Identity was determined on a SQ mass spectrometer by positive electrospray ionization. Mobile phase A consisted of either 0.01% ammonium hydroxide or 0.01% formic acid in water, while mobile phase B consisted of the same additives in acetonitrile. The gradient ran from 5% to 95% mobile phase B over 0.8 minutes at 0.45 mL/min. An Acquity BEH C18, 1.7 μm, 1.0x50 mm column was used with column temperature maintained at 65 °C.

Broad Compounds/HTS compounds that have been Screened:

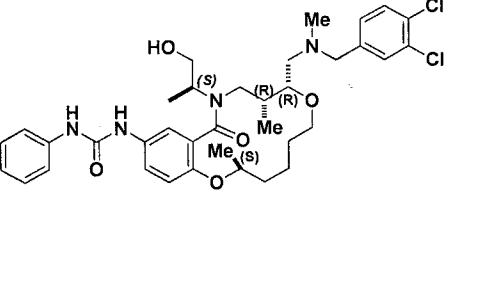
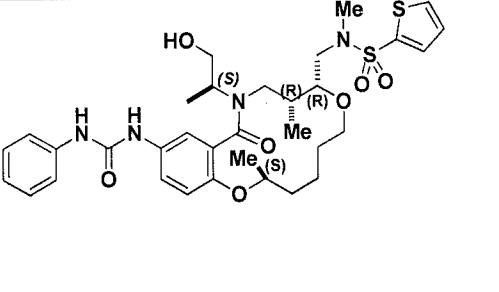
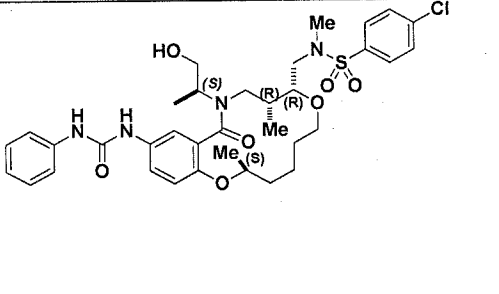
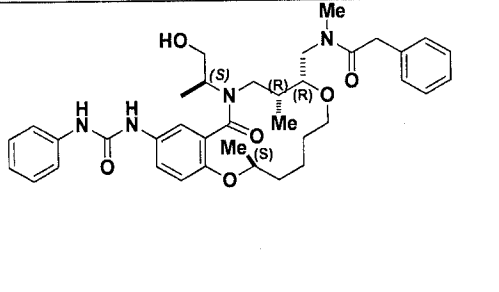
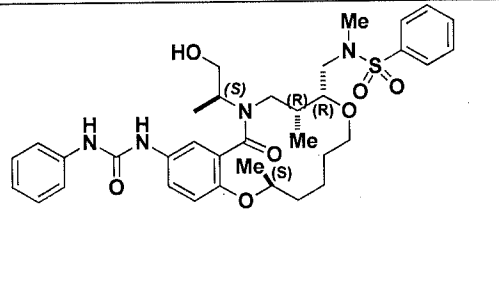
No.	Structure	Name	MS
137		1-[(2R,8R,9S)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-8-[[methyl(propyl)amino]methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-3-(propan-2-yl)urea	[M+H] ⁺ calcd, 534; found, 534

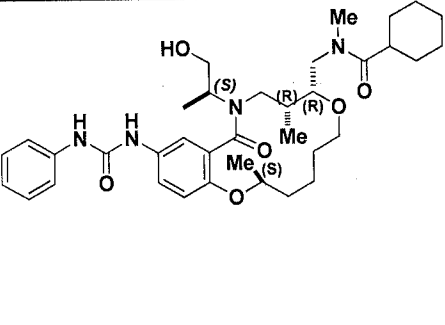
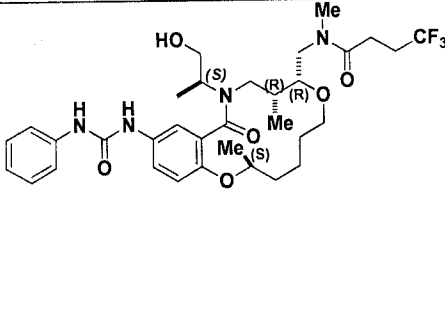
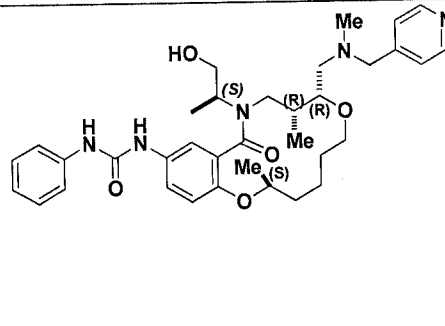
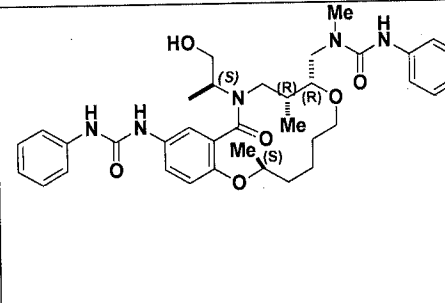
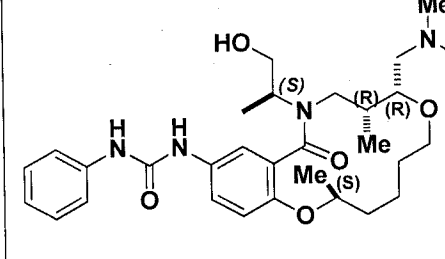
¹ Gottlieb, H. E., Kotlyar, V., Nudelman, A. *J. Org. Chem.* 1997, 62, 7512-7515.

No.	Structure	Name	MS
138		3-[[{(2R,8S,9R)-14-benzenesulfonamido-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl]methyl}-1-(4-fluorophenyl)-3-methylurea	[M+H] ⁺ calcd, 684; found, 684
139		N-[[{(2R,3S)-5-[(2S)-1-hydroxypropan-2-yl]-9-[(4-methoxybenzene)sulfonamido]-3-methyl-6-oxo-2,3,4,5,6,7-hexahydro-1,5-benzoxazonin-2-yl]methyl}-4-methoxy-N-methylbenzene-1-sulfonamide	[M+H] ⁺ calcd, 661; found, 661
140		3-[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-8-[(N-methyldimethyl-1,2-oxazole-4-sulfonamido)methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	[M+H] ⁺ calcd, 685; found, 685
141		1-[[{(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-12-oxo-14-[(phenylcarbamoyl)amino]-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl]methyl}-1-methyl-3-(naphthalen-1-yl)urea	[M+H] ⁺ calcd, 695; found, 695
142		4-[[{[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-12-oxo-14-[(phenylcarbamoyl)amino]-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl]methyl}-(methyl)amino)methyl]benzoic acid	[M+H] ⁺ calcd, 660; found, 660

No.	Structure	Name	MS
143		3-[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-8-[(N-methyl-1-methyl-1H-imidazole-4-sulfonamido)methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecine-14-yl]-1-phenylurea	[M+H] ⁺ calcd, 670; found, 670
144		3-[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-8-[[N-methyl(4-methylbenzene)sulfonamido]methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecine-14-yl]-1-phenylurea	[M+H] ⁺ calcd, 680; found, 680
145		3-[(2S,8R,9R)-8-[[cyclohexylmethyl](methyl)amino]methyl]-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecine-14-yl]-1-phenylurea	[M+H] ⁺ calcd, 622; found, 622
146		4-(dimethylamino)-N-[[2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecine-8-yl]methyl]-N-methylbutanamide	[M+H] ⁺ calcd, 639; found, 639
147		3-[(2S,8R,9R)-8-[[benzyl(methyl)amino]methyl]-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecine-14-yl]-1-phenylurea	[M+H] ⁺ calcd, 616; found, 616

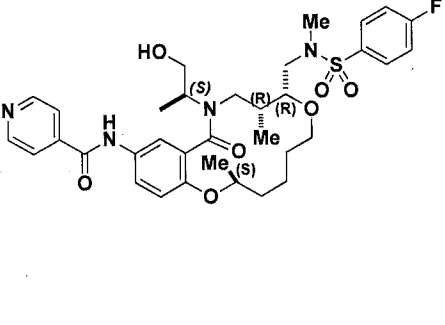
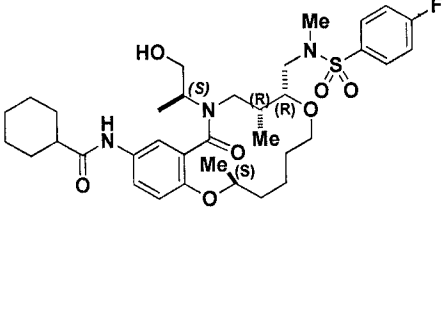
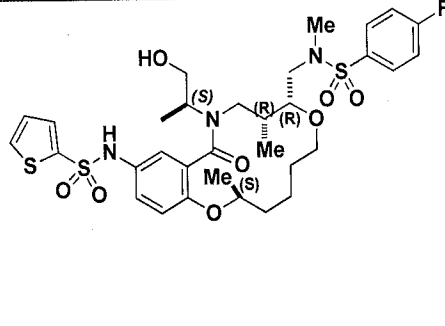
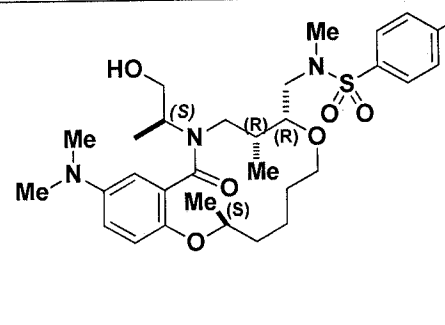
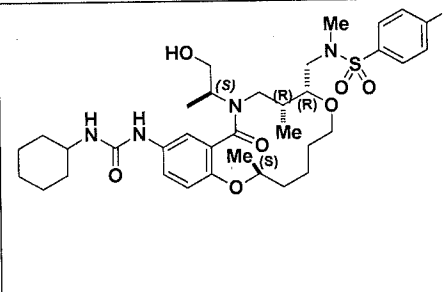
No.	Structure	Name	MS
148		3-[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-8-[[methyl({[4-(trifluoromethyl)phenyl]methyl})amino]methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	[M+H] ⁺ calcd, 684; found, 684
149		3-[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-8-[[{[4-methoxyphenyl]methyl}(methyl)amino]methyl]-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	[M+H] ⁺ calcd, 646; found, 646
150		N-[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-12-oxo-14-[(phenylcarbamoyl)amino]-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl]methyl}-N-methylbenzamide	[M+H] ⁺ calcd, 630; found, 630
151		3-[(2S,8R,9R)-8-[[{(2H-1,3-benzodioxol-5-ylmethyl)(methyl)amino]methyl]-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	[M+H] ⁺ calcd, 660; found, 660
152		3-[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-8-[[N-methyl(4-methoxybenzene)sulfonamido]methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	[M+H] ⁺ calcd, 696; found, 696

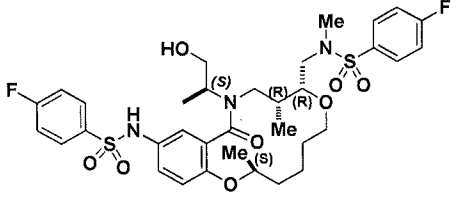
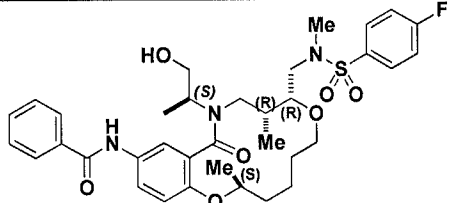
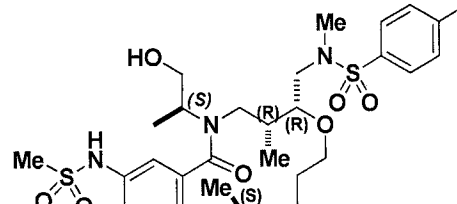
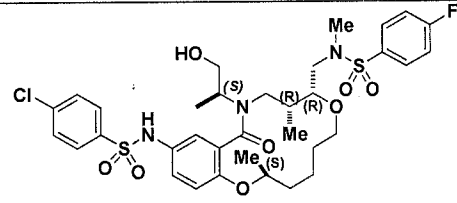
No.	Structure	Name	MS
153		3-[(2S,8R,9R)-8-([(3,4-dichlorophenyl)methyl](methyl)amino)methyl]-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	[M+H] ⁺ calcd, 684; found, 684
154		3-[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-8-[(N-methylthiophene-2-sulfonamido)methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	[M+H] ⁺ calcd, 672; found, 672
155		3-[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-8-[(N-methyl(4-chlorobenzene)sulfonamido)methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	[M+H] ⁺ calcd, 700; found, 700
156		N-([(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-12-oxo-14-[(phenylcarbamoyl)amino]-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl)methyl]-N-methyl-2-phenylacetamide	[M+H] ⁺ calcd, 644; found, 644
157		3-[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-8-[(N-methylbenzenesulfonamido)methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	[M+H] ⁺ calcd, 666; found, 666

No.	Structure	Name	MS
158		N-[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-12-oxo-14-[(phenylcarbamoyl)amino]-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl]methyl}-N-methylcyclohexanecarboxamide	[M+H] ⁺ calcd, 636; found, 636
159		4,4,4-trifluoro-N-[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-12-oxo-14-[(phenylcarbamoyl)amino]-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl]methyl}-N-methylbutanamide	[M+H] ⁺ calcd, 650; found, 650
160		3-[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-8-[[methyl(pyridin-4-ylmethyl)amino]methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	[M+H] ⁺ calcd, 617; found, 617
161		1-[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-12-oxo-14-[(phenylcarbamoyl)amino]-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl]methyl}-1-methyl-3-phenylurea	[M+H] ⁺ calcd, 645; found, 645
162		3-[(2S,8R,9R)-8-[(dimethylamino)methyl]-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	[M+H] ⁺ calcd, 540; found, 540

No.	Structure	Name	MS
163		3-[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-8-({methyl[(propan-2-yl)carbamoyl]amino}methyl)-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	[M+H] ⁺ calcd, 611; found, 611
164		1-[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-12-oxo-14-[(phenylcarbamoyl)amino]-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl]methyl}-1-methyl-3-[4-(trifluoromethyl)phenyl]urea	[M+H] ⁺ calcd, 713; found, 713
165		4,4,4-trifluoro-N-[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-8-{[N-methyl(4-fluorobenzene)sulfonamido]methyl}-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]butanamide	[M+H] ⁺ calcd, 689; found, 689
166		3-[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-8-{[N-methyl(4-fluorobenzene)sulfonamido]methyl}-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-[4-(trifluoromethyl)phenyl]urea	[M+H] ⁺ calcd, 752; found, 752
167		N-[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-8-{[N-methyl(4-fluorobenzene)sulfonamido]methyl}-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-[4-(trifluoromethyl)phenyl]urea	[M+H] ⁺ calcd, 735; found, 735

No.	Structure	Name	MS
		benzodioxazacyclotetradecan-14-yl]-4-methoxybenzene-1-sulfonamide	
168		N-[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-8-[[N-methyl(4-fluorobenzene)sulfonamido]methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecan-14-yl]-3,5-dimethyl-1,2-oxazole-4-sulfonamide	[M+H] ⁺ calcd, 724; found, 724
169		N-[[[(2S,8R,9R)-14-benzenesulfonamido-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecan-8-yl]methyl]-4-fluoro-N-methylbenzene-1-sulfonamide	[M+H] ⁺ calcd, 705; found, 705
170		N-[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-8-[[N-methyl(4-fluorobenzene)sulfonamido]methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecan-14-yl]-1-methyl-1H-imidazole-4-sulfonamide	[M+H] ⁺ calcd, 709; found, 709
171		4-fluoro-N-[[[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-14-[(4-methylbenzene)sulfonamido]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecan-8-yl]methyl]-N-methylbenzene-1-sulfonamide	[M+H] ⁺ calcd, 719; found, 719

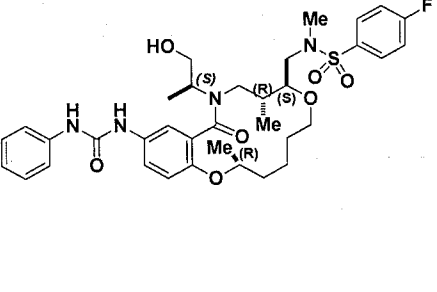
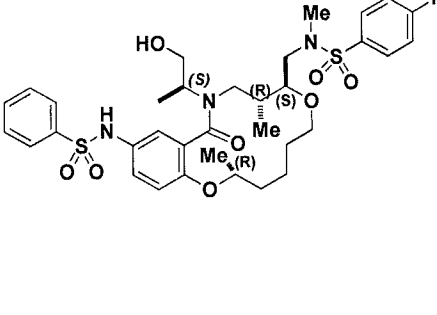
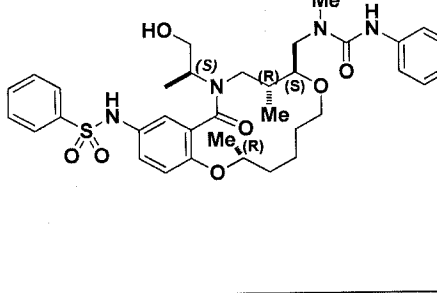
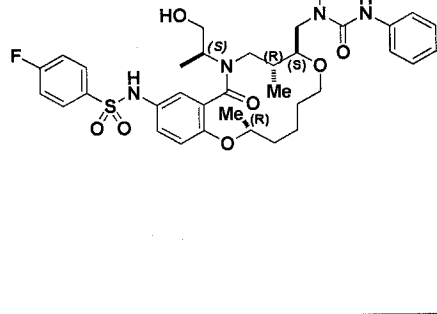
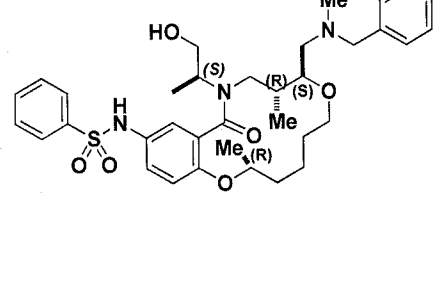
No.	Structure	Name	MS
172		N-[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-8-[[N-methyl(4-fluorobenzene)sulfonamido]methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]pyridine-4-carboxamide	[M+H] ⁺ calcd, 670; found, 670
173		N-[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-8-[[N-methyl(4-fluorobenzene)sulfonamido]methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]cyclohexanecarboxamide	[M+H] ⁺ calcd, 675; found, 675
174		N-[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-8-[[N-methyl(4-fluorobenzene)sulfonamido]methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]thiophene-2-sulfonamide	[M+H] ⁺ calcd, 711; found, 711
175		N-[(2S,8R,9R)-14-(dimethylamino)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl]methyl]-4-fluoro-N-methylbenzene-1-sulfonamide	[M+H] ⁺ calcd, 593; found, 593
176		1-cyclohexyl-3-[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-8-[[N-methyl(4-fluorobenzene)sulfonamido]methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]urea	[M+H] ⁺ calcd, 690; found, 690

No.	Structure	Name	MS
		n-14-yl]urea	
177		4-fluoro-N-{[(2S,8R,9R)-14-[(4-fluorobenzene)sulfonamido]-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl]methyl}-N-methylbenzene-1-sulfonamide	[M+H] ⁺ calcd, 723; found, 723
178		N-[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-8-{[N-methyl(4-fluorobenzene)sulfonamido]methyl}-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]benzamide	[M+H] ⁺ calcd, 669; found, 669
179		4-fluoro-N-{[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-14-methanesulfonamido-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl]methyl}-N-methylbenzene-1-sulfonamide	[M+H] ⁺ calcd, 643; found, 643
180		N-{[(2S,8R,9R)-14-[(4-chlorobenzene)sulfonamido]-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl]methyl}-4-fluoro-N-methylbenzene-1-sulfonamide	[M+H] ⁺ calcd, 739; found, 739

No.	Structure	Name	MS
181		3-[(2S,8S,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-8-[[N-methyl(4-fluorobenzene)sulfonamido]methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	[M+H] ⁺ calcd, 684; found, 684
182		3-[(2R,8R,9S)-11-[(2R)-1-hydroxypropan-2-yl]-2,9-dimethyl-8-[[N-methyl(4-fluorobenzene)sulfonamido]methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	[M+H] ⁺ calcd, 684; found, 684
183		3-[(2S,8R,9R)-11-[(2R)-1-hydroxypropan-2-yl]-2,9-dimethyl-8-[[N-methyl(4-fluorobenzene)sulfonamido]methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	[M+H] ⁺ calcd, 684; found, 684
184		3-[(2S,8R,9S)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-8-[[N-methyl(4-fluorobenzene)sulfonamido]methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	[M+H] ⁺ calcd, 684; found, 684
185		3-[(2S,8R,9S)-11-[(2R)-1-hydroxypropan-2-yl]-2,9-dimethyl-8-[[N-methyl(4-fluorobenzene)sulfonamido]methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	[M+H] ⁺ calcd, 684; found, 684

No.	Structure	Name	MS
186		3-[(2R,8S,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-8-[[N-methyl(4-fluorobenzene)sulfonamido]methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	[M+H] ⁺ calcd, 684; found, 684
187		3-[(2R,8S,9S)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-8-[[N-methyl(4-fluorobenzene)sulfonamido]methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	[M+H] ⁺ calcd, 684; found, 684
188		3-[(2S,8S,9S)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-8-[[N-methyl(4-fluorobenzene)sulfonamido]methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	[M+H] ⁺ calcd, 684; found, 684
189		3-[(2R,8R,9S)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-8-[[N-methyl(4-fluorobenzene)sulfonamido]methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	[M+H] ⁺ calcd, 684; found, 684
190		3-[(2S,8S,9R)-11-[(2R)-1-hydroxypropan-2-yl]-2,9-dimethyl-8-[[N-methyl(4-fluorobenzene)sulfonamido]methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	[M+H] ⁺ calcd, 684; found, 684

No.	Structure	Name	MS
191		3-[(2R,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-8-[[N-methyl(4-fluorobenzene)sulfonamido]methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	[M+H] ⁺ calcd, 684; found, 684
192		3-[(2S,8S,9S)-11-[(2R)-1-hydroxypropan-2-yl]-2,9-dimethyl-8-[[N-methyl(4-fluorobenzene)sulfonamido]methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	[M+H] ⁺ calcd, 684; found, 684
193		3-[(2R,8R,9R)-11-[(2R)-1-hydroxypropan-2-yl]-2,9-dimethyl-8-[[N-methyl(4-fluorobenzene)sulfonamido]methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	[M+H] ⁺ calcd, 684; found, 684
194		3-[(2R,8S,9S)-11-[(2R)-1-hydroxypropan-2-yl]-2,9-dimethyl-8-[[N-methyl(4-fluorobenzene)sulfonamido]methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	[M+H] ⁺ calcd, 684; found, 684
195		3-[(2R,8S,9R)-11-[(2R)-1-hydroxypropan-2-yl]-2,9-dimethyl-8-[[N-methyl(4-fluorobenzene)sulfonamido]methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	[M+H] ⁺ calcd, 684; found, 684

No.	Structure	Name	MS
196		1-[(2R,8S,9R)-8-({[(4-fluorophenyl)carbamoyl](methyl)amino}methyl)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-3-phenylurea	[M+H] ⁺ calcd, 663; found 663
197		N-[(2R,8S,9R)-14-benzenesulfonamido-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl]methyl}-4-fluoro-N-methylbenzene-1-sulfonamide	[M+H] ⁺ calcd, 705; found 705
198		3-[(2R,8S,9R)-14-benzenesulfonamido-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl]methyl}-3-methyl-1-phenylurea	[M+H] ⁺ calcd, 666; found 666
199		3-[(2R,8S,9R)-14-[(4-fluorobenzene)sulfonamido]-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl]methyl}-1-(4-fluorophenyl)-3-methylurea	[M+H] ⁺ calcd, 702; found 702
200		N-[(2R,8S,9R)-8-({[benzyl(methyl)amino]methyl}-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]benzenesulfonamide	[M+H] ⁺ calcd, 637; found 637

No.	Structure	Name	MS
201		1-(4-fluorophenyl)-3- {[(2R,8S,9R)-11-[(2S)-1- hydroxypropan-2-yl]-14- methanesulfonamido-2,9- dimethyl-12-oxo- 2,3,4,5,6,8,9,10,11,12- decahydro-1,7,11- benzodioxazacyclotetradeci n-8-yl)methyl]-3- methylurea	[M+H] ⁺ calcd, 622; found 622

Bioactivity table:**Key:**

- 5 * >5000 nM
 ** 500-5000nM
 *** <500 nM

Compound Number	Name	Bioactivity (Dd2)
1	4-fluoro-N-(((7R,8R,14S)-5-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-1,7,14-trimethyl-4-oxo-4,5,6,7,8,10,11,12,13,14-decahydro-1H-pyrazolo[3,4-b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)-N-methylbenzenesulfonamide	***
2	4-fluoro-N-(((6S,12R,13R)-15-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-6,13-dimethyl-16-oxo-6,7,8,9,10,12,13,14,15,16-decahydropyrazino[2,3-b][1,9,5]dioxazacyclotetradecin-12-yl)methyl)-N-methylbenzenesulfonamide	***

Compound Number	Name	Bioactivity (Dd2)
3	4-fluoro-N-(((5S,11R,12R)-14-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-5,12-dimethyl-15-oxo-5,6,7,8,9,11,12,13,14,15-decahydrothieno[3,2-b][1,9,5]dioxazacyclotetradecin-11-yl)methyl)-N-methylbenzenesulfonamide	***
4	N-(((8R,9R)-14-(3-(3,5-dimethylisoxazol-4-yl)ureido)-11-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-9-methyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1H-benzo[g][1,5,9]oxadiazacyclotetradecin-8-yl)methyl)-4-fluoro-N-methylbenzenesulfonamide	***
5	tert-butyl N-methyl-N-{(2S,8S,9R)-2,9,11-trimethyl-12-oxo-14-[(phenylcarbamoyl)amino]-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl)methyl}carbamate	*
6	1-(3,5-dimethylisoxazol-4-yl)-3-((2S,8R,9R)-11-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2,9-dimethyl-8-(morpholinomethyl)-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-14-yl)urea	**
7	N-(((2S,8R,9R)-14-(3-(3,5-dimethylisoxazol-4-yl)ureido)-11-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)-N-ethyl-4-fluorobenzenesulfonamide	NA

Compound Number	Name	Bioactivity (Dd2)
8	tert-butyl (((2S,8R,9R)-14-(3-(3,5-dimethylisoxazol-4-yl)ureido)-11-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)carbamate	NA
9	N-(((2R,8R,9R)-14-(3-(3,5-dimethylisoxazol-4-yl)ureido)-11-((S)-1-(4-methoxybenzyloxy)propan-2-yl)-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)-4-fluoro-N-methylbenzenesulfonamide	***
10	N-(((4R,5R)-15-(3-(3,5-dimethylisoxazol-4-yl)ureido)-2-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-4-methyl-1,1-dioxido-3,4,5,7,8,9,10,11-octahydro-2H-benzo[b][1,9,4,5]dioxathiaazacyclotetradecin-5-yl)methyl)-4-fluoro-N-methylbenzenesulfonamide	***
11	N-(((6R,7R)-12-(3-(3,5-dimethylisoxazol-4-yl)ureido)-9-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-7-methyl-10-oxo-2,3,4,6,7,8,9,10-octahydrobenzo[f][1,5,9]dioxazacyclododecin-6-yl)methyl)-4-fluoro-N-methylbenzenesulfonamide	NA
12	N-(((7R,8S)-13-(3-(3,5-dimethylisoxazol-4-yl)ureido)-10-((R)-1-((4-methoxybenzyl)oxy)propan-2-yl)-8-methyl-11-oxo-3,4,5,7,8,9,10,11-octahydro-2H-benzo[b][1,9,5]dioxazacyclotridecin-7-yl)methyl)-4-fluoro-N-methylbenzenesulfonamide	***

Compound Number	Name	Bioactivity (Dd2)
13	Synthesis of N-(((8R,9R)-15-(3-(3,5-dimethylisoxazol-4-yl)ureido)-11-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-9-methyl-12-oxo-3,4,5,6,8,9,10,11,12,13-decahydro-2H-benzo[h][1,10,5]dioxazacyclopentadecin-8-yl)methyl)-4-fluoro-N-methylbenzenesulfonamide	**
14	N-(((7R,8R)-14-(3-(3,5-dimethylisoxazol-4-yl)ureido)-10-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-8-methyl-11-oxo-2,3,4,5,7,8,9,10,11,12-decahydrobenzo[h][1,10,5]dioxazacyclotetradecin-7-yl)methyl)-4-fluoro-N-methylbenzenesulfonamide	**
15	N-(((5R,6R)-11-amino-8-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-6-methyl-9-oxo-3,5,6,7,8,9-hexahydro-2H-benzo[e][1,4,8]dioxazacycloundecin-5-yl)methyl)-4-fluoro-N-methylbenzenesulfonamide	NA
16	1-(3,5-dimethylisoxazol-4-yl)-3-((2S,8R,9R)-8-((1,1-dioxido-1,2-thiazinan-2-yl)methyl)-11-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-14-yl)urea	**
17	tert-butyl N-{[(2S,8R,9R)-14-cyano-11-[(2S)-1-[(4-methoxyphenyl)methoxy]propan-2-yl]-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl]methyl}-N-methylcarbamate	**

Compound Number	Name	Bioactivity (Dd2)
18	tert-butyl N-{[(2S,8R,9R)-11-[(2S)-1-[(4-methoxyphenyl)methoxy]propan-2-yl]-2,9-dimethyl-12-oxo-15-(trifluoromethyl)-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl]methyl}-N-methylcarbamate	**
19	(2S,8R,9R)-14-fluoro-11-[(2S)-1-[(4-methoxyphenyl)methoxy]propan-2-yl]-2,9-dimethyl-8-[(methylamino)methyl]-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-12-one	**
20	(2S,8R,9R)-11-[(2S)-1-[(4-methoxyphenyl)methoxy]propan-2-yl]-2,9-dimethyl-8-[(methylamino)methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecine-14-carbonitrile	*
21	(8R,9R,15S)-6-[(2S)-1-[(4-methoxyphenyl)methoxy]propan-2-yl]-8,15-dimethyl-9-[(methylamino)methyl]-5H,6H,7H,8H,9H,11H,12H,13H,14H,15H-pyrido[2,3-b]1,9-dioxo-5-azacyclotetradecan-5-one	*
22	(2S,8R,9R)-11-[(2S)-1-[(4-methoxyphenyl)methoxy]propan-2-yl]-2,9-dimethyl-8-[(methylamino)methyl]-14-(trifluoromethyl)-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-12-one	**

Compound Number	Name	Bioactivity (Dd2)
23	1-phenyl-3-[(2 <i>S</i> ,8 <i>S</i> ,9 <i>R</i>)-2,9,11-trimethyl-8-[(methylamino)methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]urea	*
24	1-(3,5-dimethylisoxazol-4-yl)-3-((2 <i>S</i> ,8 <i>R</i> ,9 <i>R</i>)-11-((<i>S</i>)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2,9-dimethyl-12-oxo-8-(piperidin-1-ylmethyl)-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[<i>b</i>][1,9,5]dioxazacyclotetradecin-14-yl)urea	**
25	3-[(2 <i>S</i> ,8 <i>R</i> ,9 <i>R</i>)-11-[(2 <i>S</i>)-1-[(4-methoxyphenyl)methoxy]propan-2-yl]-2,9-dimethyl-8-[[<i>N</i> -methyl(4-fluorobenzene)sulfonamido]methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	***
26	3-[(2 <i>S</i> ,8 <i>R</i> ,9 <i>R</i>)-11-[(2 <i>R</i>)-1-[(4-methoxyphenyl)methoxy]propan-2-yl]-2,9-dimethyl-8-[[<i>N</i> -methyl(4-fluorobenzene)sulfonamido]methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	***
27	4-fluoro- <i>N</i> -{[(8 <i>R</i> ,9 <i>R</i> ,15 <i>S</i>)-6-[(2 <i>S</i>)-1-[(4-methoxyphenyl)methoxy]propan-2-yl]-8,15-dimethyl-5-oxo-5 <i>H</i> ,6 <i>H</i> ,7 <i>H</i> ,8 <i>H</i> ,9 <i>H</i> ,11 <i>H</i> ,12 <i>H</i> ,13 <i>H</i> ,14 <i>H</i> ,15 <i>H</i> -pyrido[2,3- <i>b</i>]1,9-dioxa-5-azacyclotetradecan-9-yl]methyl}- <i>N</i> -methylbenzene-1-sulfonamide	***

Compound Number	Name	Bioactivity (Dd2)
28	4-fluoro-N-(((2S,8R,9R)-14-fluoro-11-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)-N-methylbenzenesulfonamide	***
29	N-{[(2S,8R,9R)-14-cyano-11-[(2S)-1-[(4-methoxyphenyl)methoxy]propan-2-yl]-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl)methyl]-4-fluoro-N-methylbenzene-1-sulfonamide	***
30	4-fluoro-N-{[(2S,8R,9R)-11-[(2S)-1-[(4-methoxyphenyl)methoxy]propan-2-yl]-2,9-dimethyl-12-oxo-14-(trifluoromethyl)-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl)methyl]-N-methylbenzene-1-sulfonamide	***
31	4-fluoro-N-{[(2S,8R,9R)-11-[(2S)-1-[(4-methoxyphenyl)methoxy]propan-2-yl]-2,9-dimethyl-12-oxo-15-(trifluoromethyl)-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl)methyl]-N-methylbenzene-1-sulfonamide	***
32	4-fluoro-N-{[(6S,12R,13R)-15-[(2S)-1-[(4-methoxyphenyl)methoxy]propan-2-yl]-6,13-dimethyl-16-oxo-6H,7H,8H,9H,10H,12H,13H,14H,15H,16H-pyrido[3,2-b]1,9-dioxa-5-azacyclotetradecan-12-yl)methyl]-N-methylbenzene-1-sulfonamide	***

Compound Number	Name	Bioactivity (Dd2)
33	N-(((2S,8R,9R)-14-(3-(3,5-dimethylisoxazol-4-yl)ureido)-11-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)-4-fluoro-N-methylbenzenesulfonamide	***
34	1-phenyl-3-[(2S,8S,9R)-2,9,11-trimethyl-8-{{N-methyl(4-fluorobenzene)sulfonamido}methyl}-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]urea	**
35	3-[(2S,8R,9R)-11-{2-[(4-methoxyphenyl)methoxy]ethyl}-2,9-dimethyl-8-{{N-methyl(4-fluorobenzene)sulfonamido}methyl}-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	***
36	N-[(2S,8R,9R)-2,9-dimethyl-8-{{N-methyl(4-fluorobenzene)sulfonamido}methyl}-12-oxo-11-(propan-2-yl)-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]acetamide	**
37	3-[(2S,8R,9R)-11-[(2S)-1-(tert-butoxy)propan-2-yl]-2,9-dimethyl-8-{{N-methyl(4-fluorobenzene)sulfonamido}methyl}-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	***

Compound Number	Name	Bioactivity (Dd2)
38	3-[(2S,8R,9R)-11-[(2S)-1-[(4-methoxyphenyl)methoxy]propan-2-yl]-2,9-dimethyl-8-[(N-methylmethanesulfonamido)methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	***
39	N-(((2S,8R,9R)-14-(3-(3,5-dimethylisoxazol-4-yl)ureido)-11-isopropyl-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)-4-fluoro-N-methylbenzenesulfonamide	***
40	N-(((8R,9R)-14-(3-(3,5-dimethylisoxazol-4-yl)ureido)-11-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-9-methyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)-4-fluoro-N-methylbenzenesulfonamide	***
41	N-(((2S,8R,9R)-14-(3-(3,5-dimethylisoxazol-4-yl)ureido)-11-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)-4-fluorobenzenesulfonamide	**
42	N-(((2S,8R)-14-(3-(3,5-dimethylisoxazol-4-yl)ureido)-11-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2-methyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)-4-fluoro-N-methylbenzenesulfonamide	NA
43	N-(((2S,8R,9R)-14-(3-(3,5-dimethylisoxazol-4-yl)ureido)-11-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2,9-dimethyl-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)-4-fluoro-N-methylbenzenesulfonamide	***
44	3-[(2S,8R,9R)-8-[[benzyl(methyl)amino]methyl]-11-[(2S)-1-[(4-methoxyphenyl)methoxy]propan-2-yl]-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	***

Compound Number	Name	Bioactivity (Dd2)
45	3-[(2S,8R,9R)-8-({(4-fluorophenyl)methyl}(methyl)amino)methyl)-2,9-dimethyl-12-oxo-11-(propan-2-yl)-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	**
46	3-[(2S,8R,9R)-8-{{(cyclohexylmethyl)(methyl)amino}methyl}-2,9-dimethyl-12-oxo-11-(propan-2-yl)-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	**
47	3-[(2S,8R,9R)-8-{{benzyl(methyl)amino}methyl}-2,9-dimethyl-12-oxo-11-(propan-2-yl)-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	**
48	3-[(2S,8R,9R)-8-({(4-methoxyphenyl)methyl}(methyl)amino)methyl)-2,9-dimethyl-12-oxo-11-(propan-2-yl)-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	**
49	3-[(2S,8R,9R)-8-{{(cyclohexylmethyl)(methyl)amino}methyl}-11-[(2S)-1-[(4-methoxyphenyl)methoxy]propan-2-yl]-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	***

Compound Number	Name	Bioactivity (Dd2)
50	1-((2S,8R,9R)-8-(((4-methoxybenzyl)(methyl)amino)methyl)-11-((S)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-14-yl)-3-phenylurea	***
51	(2S)-2-[(2S,8R,9R)-8-({[(tert-butoxy)carbonyl](methyl)amino}methyl)-2,9-dimethyl-12-oxo-14-[(phenylcarbamoyl)amino]-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-11-yl]propyl benzoate	**
52	3-[(2S,8R,9R)-2,9-dimethyl-8-{{[N-methyl(4-fluorobenzene)sulfonamido]methyl}-12-oxo-11-(propan-2-yl)-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	***
53	3-[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-8-{{[N-methyl(4-fluorobenzene)sulfonamido]methyl}-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	***
54	3-[(2S,8R,9R)-11-[(2R)-1-hydroxypropan-2-yl]-2,9-dimethyl-8-{{[N-methyl(4-fluorobenzene)sulfonamido]methyl}-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	***
55	4-fluoro-N-{{[(8R,9R,15S)-6-[(2S)-1-hydroxypropan-2-yl]-8,15-dimethyl-5-oxo-5H,6H,7H,8H,9H,11H,12H,13H,14H,15H-pyrido[2,3-b]1,9-dioxo-5-azacyclotetradecan-9-yl]methyl}-N-methylbenzene-1-sulfonamide	*

Compound Number	Name	Bioactivity (Dd2)
56	4-fluoro-N-[[[(2S,8R,9R)-14-fluoro-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl]methyl]-N-methylbenzene-1-sulfonamide	*
57	4-fluoro-N-[[[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-12-oxo-14-(trifluoromethyl)-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl]methyl]-N-methylbenzene-1-sulfonamide	**
58	N-[[[(2S,8R,9R)-14-cyano-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl]methyl]-4-fluoro-N-methylbenzene-1-sulfonamide	*
59	4-fluoro-N-[[[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-12-oxo-15-(trifluoromethyl)-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl]methyl]-N-methylbenzene-1-sulfonamide	**
60	4-fluoro-N-[[[(6S,12R,13R)-15-[(2S)-1-hydroxypropan-2-yl]-6,13-dimethyl-16-oxo-6H,7H,8H,9H,10H,12H,13H,14H,15H,16H-pyrido[3,2-b]1,9-dioxo-5-azacyclotetradecan-12-yl]methyl]-N-methylbenzene-1-sulfonamide	*
61	1-[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-8-[[N-methyl(4-fluorobenzene)sulfonamido]methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-3-(propan-2-yl)urea	***
62	3-[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-8-([N-methyl[4-(trifluoromethyl)benzene]sulfonamido)methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	**
63	3-[(2S,8R,9R)-11-(2-hydroxyethyl)-2,9-dimethyl-8-[[N-methyl(4-fluorobenzene)sulfonamido]methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	**

Compound Number	Name	Bioactivity (Dd2)
64 E/Z	3-[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-8-[[N-methyl(4-fluorobenzene)sulfonamido]methyl]-12-oxo-2,3,6,8,9,10,11,12-octahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	***
65 E/Z	3-[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-8-[[N-methyl(4-fluorobenzene)sulfonamido]methyl]-12-oxo-2,3,6,8,9,10,11,12-octahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	***
66	phenyl N-[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-12-oxo-14-[(phenylcarbamoyl)amino]-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl)methyl]-N-methylcarbamate	*
67	2-methoxyethyl N-[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-12-oxo-14-[(phenylcarbamoyl)amino]-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl)methyl]-N-methylcarbamate	*
68	N-(((8R,9R)-14-(3-(3,5-dimethylisoxazol-4-yl)ureido)-11-((S)-1-hydroxypropan-2-yl)-9-methyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)-4-fluoro-N-methylbenzenesulfonamide	NA
69	N-(((2R,8R,9R)-14-(3-(3,5-dimethylisoxazol-4-yl)ureido)-11-((S)-1-hydroxypropan-2-yl)-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)-4-fluoro-N-methylbenzenesulfonamide	NA
70	4-fluoro-N-(((8R,9R)-11-((S)-1-hydroxypropan-2-yl)-9-methyl-14-nitro-12-oxo-2,3,6,8,9,10,11,12-octahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)-N-methylbenzenesulfonamide	NA
71	R)-2-((2S,8R,9R)-8-(((allyloxy)carbonyl(methyl)amino)methyl)-2,9-dimethyl-12-oxo-14-(3-phenylureido)-3,4,5,6,9,10-hexahydrobenzo[b][1,9,5]dioxazacyclotetradecin-11(2H,8H,12H)-yl)propyl benzoate	**

Compound Number	Name	Bioactivity (Dd2)
72	(2S)-2-[(2S,8R,9R)-2,9-dimethyl-8-[[N-methyl(4-fluorobenzene)sulfonamido]methyl]-12-oxo-14-[(phenylcarbamoyl)amino]-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-11-yl]propyl benzoate	***
73	prop-2-en-1-yl N-[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-12-oxo-14-[(phenylcarbamoyl)amino]-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl]methyl}-N-methylcarbamate	**
74	prop-2-en-1-yl N-[(2S,8R,9R)-11-[(2R)-1-hydroxypropan-2-yl]-2,9-dimethyl-12-oxo-14-[(phenylcarbamoyl)amino]-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl]methyl}-N-methylcarbamate	*
75	tert-butyl N-[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-12-oxo-14-[(phenylcarbamoyl)amino]-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl]methyl}-N-methylcarbamate	**
76	N-[(2S,8R,9R)-14-[(1,3-benzoxazol-2-yl)amino]-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl]methyl}-4-fluoro-N-methylbenzene-1-sulfonamide	**
77	3-(dimethyl-1,2-oxazol-4-yl)-1-[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-8-[[N-methyl(4-fluorobenzene)sulfonamido]methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]urea	***
78	1-[(2S,8R,9R)-8-(((4-fluorobenzyl)(methyl)amino)methyl)-11-((S)-1-hydroxypropan-2-yl)-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-14-yl)-3-phenylurea	**
79	9H-fluoren-9-ylmethyl N-[(2S,8R,9R)-11-[(2S)-1-[(tert-butyl)dimethylsilyl]oxy]propan-2-yl]-2,9-dimethyl-8-[(methyl[(prop-2-en-1-yloxy)carbonyl]amino)methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]carbamate	*

Compound Number	Name	Bioactivity (Dd2)
80	prop-2-en-1-yl N-{{(2S,8S,9R)-11-[(2S)-1-[(tert-butyl dimethylsilyl)oxy]propan-2-yl]-2,9-dimethyl-12-oxo-14-[(phenylcarbamoyl)amino]-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl)methyl}-N-methylcarbamate	**
81	3-[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-8-[[N-methyl(2-fluorobenzene)sulfonamido]methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	**
82	3-[(2S,8S,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-8-[(methylamino)methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	*
83	3-[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-8-[[N-methyl(3-fluorobenzene)sulfonamido]methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	**
84	3-[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-8-[(N-methylpyridine-3-sulfonamido)methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	*
85	benzyl N-{{(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-12-oxo-14-[(phenylcarbamoyl)amino]-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl)methyl}-N-methylcarbamate	*
86	propyl N-{{(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-12-oxo-14-[(phenylcarbamoyl)amino]-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl)methyl}-N-methylcarbamate	*
87	N-[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-8-[[N-methyl(4-fluorobenzene)sulfonamido]methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]acetamide	*

Compound Number	Name	Bioactivity (Dd2)
88	N-{[(2S,8R,9R)-14-amino-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl)methyl]-4-fluoro-N-methylbenzene-1-sulfonamide	***
89	N-(((2S,8R,9R)-11-((S)-1-azidopropan-2-yl)-2,9-dimethyl-12-oxo-14-(3-phenylureido)-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)-4-fluoro-N-methylbenzenesulfonamide	***
90	N-{(2S,8R,9R)-11-[(2S)-1-azidopropan-2-yl]-14-fluoro-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl)methyl}-4-fluoro-N-methylbenzene-1-sulfonamide	**
91	N-{[(2S,8R,9R)-11-[(2S)-1-azidopropan-2-yl]-14-cyano-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl)methyl]-4-fluoro-N-methylbenzene-1-sulfonamide	**
92	N-{(6S,12R,13R)-15-[(2S)-1-azidopropan-2-yl]-6,13-dimethyl-16-oxo-6H,7H,8H,9H,10H,12H,13H,14H,15H,16H-pyrido[3,2-b]1,9-dioxa-5-azacyclotetradecan-12-yl)methyl}-4-fluoro-N-methylbenzene-1-sulfonamide	**
93	N-{[(2S,8R,9R)-11-[(2S)-1-azidopropan-2-yl]-2,9-dimethyl-12-oxo-15-(trifluoromethyl)-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl)methyl]-4-fluoro-N-methylbenzene-1-sulfonamide	***
94	3-[(2S,8R,9R)-11-[(2S)-1-aminopropan-2-yl]-2,9-dimethyl-8-{[N-methyl(4-fluorobenzene)sulfonamido]methyl}-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	***
95	3-[(2S,8R,9R)-2,9-dimethyl-8-{[N-methyl(4-fluorobenzene)sulfonamido]methyl}-11-[(2S)-1-(methylamino)propan-2-yl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	***

Compound Number	Name	Bioactivity (Dd2)
96	3-[(2S,8R,9R)-2,9-dimethyl-8-[[N-methyl(4-fluorobenzene)sulfonamido]methyl]-11-[(2R)-1-(methylamino)propan-2-yl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	**
97	N-[[[(2S,8R,9R)-2,9-dimethyl-11-[(2S)-1-(methylamino)propan-2-yl]-12-oxo-14-(trifluoromethyl)-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl]methyl]-4-fluoro-N-methylbenzene-1-sulfonamide	**
98	4-fluoro-N-[[[(2S,8R,9R)-14-fluoro-2,9-dimethyl-11-[(2S)-1-(methylamino)propan-2-yl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl]methyl]-N-methylbenzene-1-sulfonamide	**
99	N-(((8R,9R)-14-(3-(3,5-dimethylisoxazol-4-yl)ureido)-9-methyl-11-((S)-1-(methylamino)propan-2-yl)-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)-4-fluoro-N-methylbenzenesulfonamide	**
100	3-[(2S,8R,9R)-11-[(2S)-1-(dimethylamino)propan-2-yl]-2,9-dimethyl-8-[[N-methyl(4-fluorobenzene)sulfonamido]methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	***
101	N-[[[(2S,8R,9R)-11-[(2S)-1-(dimethylamino)propan-2-yl]-2,9-dimethyl-12-oxo-14-(trifluoromethyl)-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl]methyl]-4-fluoro-N-methylbenzene-1-sulfonamide	**
102	N-[[[(2S,8R,9R)-11-[(2S)-1-(dimethylamino)propan-2-yl]-14-fluoro-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl]methyl]-4-fluoro-N-methylbenzene-1-sulfonamide	**
103	N-(((2S,8R,9R)-11-((R)-1-(dimethylamino)propan-2-yl)-2,9-dimethyl-12-oxo-14-(3-phenylureido)-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)-4-fluoro-N-methylbenzenesulfonamide	**

Compound Number	Name	Bioactivity (Dd2)
104	3-(dimethyl-1,2-oxazol-4-yl)-1-[(2S,8R,9R)-11-[(2S)-1-(dimethylamino)propan-2-yl]-2,9-dimethyl-8-[[N-methyl(4-fluorobenzene)sulfonamido]methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]urea	***
105	N-(((8R,9R)-11-((S)-1-(dimethylamino)propan-2-yl)-14-(3-(3,5-dimethylisoxazol-4-yl)ureido)-9-methyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)-4-fluoro-N-methylbenzenesulfonamide	***
106	N-(((8R,9R,15S)-6-((S)-1-aminopropan-2-yl)-8,15-dimethyl-5-oxo-5,6,7,8,9,11,12,13,14,15-decahydropyrido[2,3-b][1,9,5]dioxazacyclotetradecin-9-yl)methyl)-4-fluoro-N-methylbenzenesulfonamide	**
107	N-(((2S,8R,9R)-11-((S)-1-aminopropan-2-yl)-2,9-dimethyl-12-oxo-15-(trifluoromethyl)-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)-4-fluoro-N-methylbenzenesulfonamide	***
108	N-(((8R,9R,15S)-8,15-dimethyl-6-((S)-1-(methylamino)propan-2-yl)-5-oxo-5,6,7,8,9,11,12,13,14,15-decahydropyrido[2,3-b][1,9,5]dioxazacyclotetradecin-9-yl)methyl)-4-fluoro-N-methylbenzenesulfonamide	***
109	N-(((2S,8R,9R)-2,9-dimethyl-11-((S)-1-(methylamino)propan-2-yl)-12-oxo-15-(trifluoromethyl)-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)-4-fluoro-N-methylbenzenesulfonamide	***
110	N-(((8R,9R,15S)-6-((S)-1-(dimethylamino)propan-2-yl)-8,15-dimethyl-5-oxo-5,6,7,8,9,11,12,13,14,15-decahydropyrido[2,3-b][1,9,5]dioxazacyclotetradecin-9-yl)methyl)-4-fluoro-N-methylbenzenesulfonamide	***
111	N-{[(2S,8R,9R)-11-[(2S)-1-(dimethylamino)propan-2-yl]-2,9-dimethyl-12-oxo-15-(trifluoromethyl)-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl]methyl}-4-fluoro-N-methylbenzene-1-sulfonamide	***

Compound Number	Name	Bioactivity (Dd2)
112	N-(((8R,9R,15S)-6-((S)-1-((2,4-difluorobenzyl)(methyl)amino)propan-2-yl)-8,15-dimethyl-5-oxo-5,6,7,8,9,11,12,13,14,15-decahydropyrido[2,3-b][1,9,5]dioxazaacyclotetradecin-9-yl)methyl)-4-fluoro-N-methylbenzenesulfonamide	*
113	3-[(2S,8R,9R)-2,9-dimethyl-8-{{N-methyl(4-fluorobenzene)sulfonamido}methyl}-12-oxo-11-[(2S)-1-(pyridin-3-yloxy)propan-2-yl]-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	***
114	3-[(2S,8R,9R)-2,9-dimethyl-8-{{N-methyl(4-fluorobenzene)sulfonamido}methyl}-12-oxo-11-[(2S)-1-(pyridin-2-yloxy)propan-2-yl]-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	***
115	3-[(2S,8R,9R)-11-[(2S)-1-methoxypropan-2-yl]-2,9-dimethyl-8-{{N-methyl(4-fluorobenzene)sulfonamido}methyl}-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	**
116	3-[(2S,8R,9R)-11-[(2S)-1-(methoxymethoxy)propan-2-yl]-2,9-dimethyl-8-{{N-methyl(4-fluorobenzene)sulfonamido}methyl}-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	***
117	3-[(2S,8R,9R)-11-[(2S)-1-[(2-methoxyethoxy)methoxy]propan-2-yl]-2,9-dimethyl-8-{{N-methyl(4-fluorobenzene)sulfonamido}methyl}-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	***
118	3-[(2S,8R,9R)-11-[(2S)-1-[(tert-butyldimethylsilyl)oxy]propan-2-yl]-2,9-dimethyl-8-{{N-methyl(4-fluorobenzene)sulfonamido}methyl}-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	***
119	3-[(2S,8R,9R)-11-{2-[(tert-butyldimethylsilyl)oxy]ethyl}-2,9-dimethyl-8-{{N-methyl(4-fluorobenzene)sulfonamido}methyl}-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	***

Compound Number	Name	Bioactivity (Dd2)
120	3-[(2S,8R,9R)-11-[(2R)-1-[(tert-butyldimethylsilyl)oxy]propan-2-yl]-2,9-dimethyl-8-[[N-methyl(4-fluorobenzene)sulfonamido]methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	***
121	(2S)-2-[(2S,8R,9R)-2,9-dimethyl-8-[[N-methyl(4-fluorobenzene)sulfonamido]methyl]-12-oxo-14-[(phenylcarbamoyl)amino]-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-11-yl]propyl 4-methylbenzene-1-sulfonate	***
122	(2S)-2-[(2S,8R,9R)-2,9-dimethyl-8-[[N-methyl(4-fluorobenzene)sulfonamido]methyl]-12-oxo-14-[(phenylcarbamoyl)amino]-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-11-yl]propyl 2,2-dimethylpropanoate	***
123	4-fluoro-N-methyl-N-(((8R,9R,E)-9-methyl-14-nitro-12-oxo-11-((2S)-1-(((3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)propan-2-yl)-2,3,6,8,9,10,11,12-octahydrobenzo[b][1,9,5]dioxazacyclotetradecin-8-yl)methyl)benzenesulfonamide	NA
124	3-[(2S,8R,9R)-11-[(2S)-1-(4-tert-butyl-1H-1,2,3-triazol-1-yl)propan-2-yl]-2,9-dimethyl-8-[[N-methyl(4-fluorobenzene)sulfonamido]methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	**
125	3-[(2S,8R,9R)-11-[(2S)-1-[4-(methoxymethyl)-1H-1,2,3-triazol-1-yl]propan-2-yl]-2,9-dimethyl-8-[[N-methyl(4-fluorobenzene)sulfonamido]methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	***
126	3-[(2S,8R,9R)-11-[(2S)-1-(4-cyclopropyl-1H-1,2,3-triazol-1-yl)propan-2-yl]-2,9-dimethyl-8-[[N-methyl(4-fluorobenzene)sulfonamido]methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	***
127	N-[(2S)-2-[(2S,8R,9R)-2,9-dimethyl-8-[[N-methyl(4-fluorobenzene)sulfonamido]methyl]-12-oxo-14-[(phenylcarbamoyl)amino]-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-11-yl]propyl]-2,2-dimethylpropanamide	***

Compound Number	Name	Bioactivity (Dd2)
128	N-[(2S)-2-[(2S,8R,9R)-2,9-dimethyl-8-[[N-methyl(4-fluorobenzene)sulfonamido]methyl]-12-oxo-14-[(phenylcarbamoyl)amino]-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-11-yl]propyl]acetamide	**
129	ethyl N-[(2S)-2-[(2S,8R,9R)-2,9-dimethyl-8-[[N-methyl(4-fluorobenzene)sulfonamido]methyl]-12-oxo-14-[(phenylcarbamoyl)amino]-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-11-yl]propyl]carbamate	***
130	3-[(2S,8R,9R)-11-[(2S)-1-[(ethylcarbamoyl)amino]propan-2-yl]-2,9-dimethyl-8-[[N-methyl(4-fluorobenzene)sulfonamido]methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	***
131	N-[(2S,8R,9R)-2,9-dimethyl-12-oxo-11-(propan-2-yl)-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl]methyl]-4-fluoro-N-methylbenzene-1-sulfonamide	**
132	4-fluoro-N-[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl]methyl]-N-methylbenzene-1-sulfonamide	**
133	(2S)-2-[(2S,8R,9R)-14-fluoro-2,9-dimethyl-8-[[N-methyl(4-fluorobenzene)sulfonamido]methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-11-yl]-N,N-dimethylpropanamine oxide	*
134	4-fluoro-N-[(2S,8R,9R)-11-[(2S)-1-[(4-methoxyphenyl)methoxy]propan-2-yl]-2,9-dimethyl-12-oxo-14-(1H-1,2,3,4-tetrazol-5-yl)-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl]methyl]-N-methylbenzene-1-sulfonamide	***
135	3-[(2S,8R,9R)-2,9-dimethyl-8-[[N-methyl(4-fluorobenzene)sulfonamido]methyl]-11-(propan-2-yl)-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	**

Compound Number	Name	Bioactivity (Dd2)
136	N-{{(2S,8R,9R)-14-(dimethylamino)-2,9-dimethyl-12-oxo-11-(propan-2-yl)-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl)methyl}-4-fluoro-N-methylbenzene-1-sulfonamide	**
137	1-[(2R,8R,9S)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-8-{{methyl(propyl)amino)methyl}-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-3-(propan-2-yl)urea	*
138	3-{{(2R,8S,9R)-14-benzenesulfonamido-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl)methyl}-1-(4-fluorophenyl)-3-methylurea	**
139	N-{{(2R,3S)-5-[(2S)-1-hydroxypropan-2-yl]-9-[(4-methoxybenzene)sulfonamido]-3-methyl-6-oxo-2,3,4,5,6,7-hexahydro-1,5-benzoxazonin-2-yl)methyl}-4-methoxy-N-methylbenzene-1-sulfonamide	**
140	3-[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-8-[(N-methyldimethyl-1,2-oxazole-4-sulfonamido)methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	**
141	1-{{(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-12-oxo-14-[(phenylcarbamoyl)amino]-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl)methyl}-1-methyl-3-(naphthalen-1-yl)urea	**
142	4-[[[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-12-oxo-14-[(phenylcarbamoyl)amino]-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl)methyl](methyl)amino)methyl]benzoic acid	*
143	3-[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-8-[(N-methyl-1-methyl-1H-imidazole-4-sulfonamido)methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	*

Compound Number	Name	Bioactivity (Dd2)
144	3-[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-8-[[N-methyl(4-methylbenzene)sulfonamido]methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	***
145	3-[(2S,8R,9R)-8-[(cyclohexylmethyl)(methyl)amino]methyl]-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	**
146	4-(dimethylamino)-N-[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-12-oxo-14-[(phenylcarbamoyl)amino]-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl]methyl]-N-methylbutanamide	*
147	3-[(2S,8R,9R)-8-[(benzyl(methyl)amino]methyl]-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	**
148	3-[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-8-[[methyl(4-(trifluoromethyl)phenyl)methyl]amino]methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	**
149	3-[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-8-[(4-methoxyphenyl)methyl](methyl)amino]methyl]-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	**
150	N-[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-12-oxo-14-[(phenylcarbamoyl)amino]-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl]methyl]-N-methylbenzamide	**
151	3-[(2S,8R,9R)-8-[(2H-1,3-benzodioxol-5-ylmethyl)(methyl)amino]methyl]-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	**

Compound Number	Name	Bioactivity (Dd2)
152	3-[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-8- {[N-methyl(4-methoxybenzene)sulfonamido]methyl}-12-oxo- 2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11- benzodioxazacyclotetradecin-14-yl]-1-phenylurea	**
153	3-[(2S,8R,9R)-8-({(3,4- dichlorophenyl)methyl}(methyl)amino)methyl)-11-[(2S)-1- hydroxypropan-2-yl]-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12- decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1- phenylurea	**
154	3-[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-8- [(N-methylthiophene-2-sulfonamido)methyl]-12-oxo- 2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11- benzodioxazacyclotetradecin-14-yl]-1-phenylurea	***
155	3-[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-8- {[N-methyl(4-chlorobenzene)sulfonamido]methyl}-12-oxo- 2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11- benzodioxazacyclotetradecin-14-yl]-1-phenylurea	**
156	N-{[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl- 12-oxo-14-[(phenylcarbamoyl)amino]-2,3,4,5,6,8,9,10,11,12- decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl]methyl}-N- methyl-2-phenylacetamide	*
157	3-[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-8- [(N-methylbenzenesulfonamido)methyl]-12-oxo- 2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11- benzodioxazacyclotetradecin-14-yl]-1-phenylurea	***
158	N-{[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl- 12-oxo-14-[(phenylcarbamoyl)amino]-2,3,4,5,6,8,9,10,11,12- decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl]methyl}-N- methylcyclohexanecarboxamide	**
159	4,4,4-trifluoro-N-{[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]- 2,9-dimethyl-12-oxo-14-[(phenylcarbamoyl)amino]- 2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11- benzodioxazacyclotetradecin-8-yl]methyl}-N-methylbutanamide	*

Compound Number	Name	Bioactivity (Dd2)
160	3-[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-8- {[methyl(pyridin-4-ylmethyl)amino]methyl}-12-oxo- 2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11- benzodioxazacyclotetradecin-14-yl]-1-phenylurea	**
161	1-{[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-12- oxo-14-[(phenylcarbamoyl)amino]-2,3,4,5,6,8,9,10,11,12- decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl]methyl}-1- methyl-3-phenylurea	*
162	3-[(2S,8R,9R)-8-[(dimethylamino)methyl]-11-[(2S)-1- hydroxypropan-2-yl]-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12- decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1- phenylurea	*
163	3-[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-8- {[methyl[(propan-2-yl)carbamoyl]amino]methyl}-12-oxo- 2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11- benzodioxazacyclotetradecin-14-yl]-1-phenylurea	*
164	1-{[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-12- oxo-14-[(phenylcarbamoyl)amino]-2,3,4,5,6,8,9,10,11,12- decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl]methyl}-1- methyl-3-[4-(trifluoromethyl)phenyl]urea	*
165	4,4,4-trifluoro-N-[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]- 2,9-dimethyl-8-[[N-methyl(4- fluorobenzene)sulfonamido]methyl]-12-oxo- 2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11- benzodioxazacyclotetradecin-14-yl]butanamide	**
166	3-[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-8- {[N-methyl(4-fluorobenzene)sulfonamido]methyl}-12-oxo- 2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11- benzodioxazacyclotetradecin-14-yl]-1-[4- (trifluoromethyl)phenyl]urea	**
167	N-[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-8- {[N-methyl(4-fluorobenzene)sulfonamido]methyl}-12-oxo- 2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11- benzodioxazacyclotetradecin-14-yl]-4-methoxybenzene-1- sulfonamide	*

Compound Number	Name	Bioactivity (Dd2)
168	N-[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-8-[[N-methyl(4-fluorobenzene)sulfonamido]methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-3,5-dimethyl-1,2-oxazole-4-sulfonamide	**
169	N-[[[(2S,8R,9R)-14-benzenesulfonamido-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl]methyl]-4-fluoro-N-methylbenzene-1-sulfonamide	**
170	N-[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-8-[[N-methyl(4-fluorobenzene)sulfonamido]methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-methyl-1H-imidazole-4-sulfonamide	*
171	4-fluoro-N-[[[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-14-[(4-methylbenzene)sulfonamido]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl]methyl]-N-methylbenzene-1-sulfonamide	*
172	N-[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-8-[[N-methyl(4-fluorobenzene)sulfonamido]methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]pyridine-4-carboxamide	**
173	N-[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-8-[[N-methyl(4-fluorobenzene)sulfonamido]methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]cyclohexanecarboxamide	**
174	N-[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-8-[[N-methyl(4-fluorobenzene)sulfonamido]methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]thiophene-2-sulfonamide	*
175	N-[[[(2S,8R,9R)-14-(dimethylamino)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl]methyl]-4-fluoro-N-methylbenzene-1-sulfonamide	*

Compound Number	Name	Bioactivity (Dd2)
176	1-cyclohexyl-3-[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-8-[[N-methyl(4-fluorobenzene)sulfonamido]methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]urea	**
177	4-fluoro-N-[(2S,8R,9R)-14-[(4-fluorobenzene)sulfonamido]-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl]methyl}-N-methylbenzene-1-sulfonamide	**
178	N-[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-8-[[N-methyl(4-fluorobenzene)sulfonamido]methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]benzamide	**
179	4-fluoro-N-[(2S,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-14-methanesulfonamido-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl]methyl}-N-methylbenzene-1-sulfonamide	*
180	N-[(2S,8R,9R)-14-[(4-chlorobenzene)sulfonamido]-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl]methyl}-4-fluoro-N-methylbenzene-1-sulfonamide	*
181	3-[(2S,8S,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-8-[[N-methyl(4-fluorobenzene)sulfonamido]methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	**
182	3-[(2R,8R,9S)-11-[(2R)-1-hydroxypropan-2-yl]-2,9-dimethyl-8-[[N-methyl(4-fluorobenzene)sulfonamido]methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	**
183	3-[(2S,8R,9R)-11-[(2R)-1-hydroxypropan-2-yl]-2,9-dimethyl-8-[[N-methyl(4-fluorobenzene)sulfonamido]methyl]-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-1-phenylurea	***

Compound Number	Name	Bioactivity (Dd2)
184	3-[(2S,8R,9S)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-8- {[N-methyl(4-fluorobenzene)sulfonamido]methyl}-12-oxo- 2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11- benzodioxazacyclotetradecin-14-yl]-1-phenylurea	**
185	3-[(2S,8R,9S)-11-[(2R)-1-hydroxypropan-2-yl]-2,9-dimethyl-8- {[N-methyl(4-fluorobenzene)sulfonamido]methyl}-12-oxo- 2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11- benzodioxazacyclotetradecin-14-yl]-1-phenylurea	*
186	3-[(2R,8S,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-8- {[N-methyl(4-fluorobenzene)sulfonamido]methyl}-12-oxo- 2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11- benzodioxazacyclotetradecin-14-yl]-1-phenylurea	**
187	3-[(2R,8S,9S)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-8- {[N-methyl(4-fluorobenzene)sulfonamido]methyl}-12-oxo- 2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11- benzodioxazacyclotetradecin-14-yl]-1-phenylurea	**
188	3-[(2S,8S,9S)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-8- {[N-methyl(4-fluorobenzene)sulfonamido]methyl}-12-oxo- 2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11- benzodioxazacyclotetradecin-14-yl]-1-phenylurea	**
189	3-[(2R,8R,9S)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-8- {[N-methyl(4-fluorobenzene)sulfonamido]methyl}-12-oxo- 2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11- benzodioxazacyclotetradecin-14-yl]-1-phenylurea	**
190	3-[(2S,8S,9R)-11-[(2R)-1-hydroxypropan-2-yl]-2,9-dimethyl-8- {[N-methyl(4-fluorobenzene)sulfonamido]methyl}-12-oxo- 2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11- benzodioxazacyclotetradecin-14-yl]-1-phenylurea	**
191	3-[(2R,8R,9R)-11-[(2S)-1-hydroxypropan-2-yl]-2,9-dimethyl-8- {[N-methyl(4-fluorobenzene)sulfonamido]methyl}-12-oxo- 2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11- benzodioxazacyclotetradecin-14-yl]-1-phenylurea	*

Compound Number	Name	Bioactivity (Dd2)
192	3-[(2S,8S,9S)-11-[(2R)-1-hydroxypropan-2-yl]-2,9-dimethyl-8- {{N-methyl(4-fluorobenzene)sulfonamido)methyl}-12-oxo- 2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11- benzodioxazacyclotetradecin-14-yl]-1-phenylurea	**
193	3-[(2R,8R,9R)-11-[(2R)-1-hydroxypropan-2-yl]-2,9-dimethyl-8- {{N-methyl(4-fluorobenzene)sulfonamido)methyl}-12-oxo- 2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11- benzodioxazacyclotetradecin-14-yl]-1-phenylurea	*
194	3-[(2R,8S,9S)-11-[(2R)-1-hydroxypropan-2-yl]-2,9-dimethyl-8- {{N-methyl(4-fluorobenzene)sulfonamido)methyl}-12-oxo- 2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11- benzodioxazacyclotetradecin-14-yl]-1-phenylurea	**
195	3-[(2R,8S,9R)-11-[(2R)-1-hydroxypropan-2-yl]-2,9-dimethyl-8- {{N-methyl(4-fluorobenzene)sulfonamido)methyl}-12-oxo- 2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11- benzodioxazacyclotetradecin-14-yl]-1-phenylurea	*
196	1-[(2R,8S,9R)-8-({[(4- fluorophenyl)carbamoyl](methyl)amino)methyl)-11-[(2S)-1- hydroxypropan-2-yl]-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12- decahydro-1,7,11-benzodioxazacyclotetradecin-14-yl]-3- phenylurea	**
197	N-[(2R,8S,9R)-14-benzenesulfonamido-11-[(2S)-1- hydroxypropan-2-yl]-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12- decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl)methyl]-4- fluoro-N-methylbenzene-1-sulfonamide	**
198	3-[(2R,8S,9R)-14-benzenesulfonamido-11-[(2S)-1- hydroxypropan-2-yl]-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12- decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl)methyl]-3- methyl-1-phenylurea	**
199	3-[(2R,8S,9R)-14-[(4-fluorobenzene)sulfonamido]-11-[(2S)-1- hydroxypropan-2-yl]-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12- decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl)methyl]-1- (4-fluorophenyl)-3-methylurea	**
200	N-[(2R,8S,9R)-8-({benzyl(methyl)amino)methyl)-11-[(2S)-1- hydroxypropan-2-yl]-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12- decahydro-1,7,11-benzodioxazacyclotetradecin-14- yl]benzenesulfonamide	**

Compound Number	Name	Bioactivity (Dd2)
201	1-(4-fluorophenyl)-3-{[(2R,8S,9R)-11-[(2S)-1-hydroxypropan-2-yl]-14-methanesulfonamido-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydro-1,7,11-benzodioxazacyclotetradecin-8-yl)methyl}-3-methylurea	**

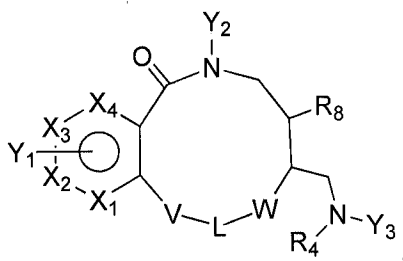
While this invention has been particularly shown and described with references to example embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

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CLAIMS

What is claimed is:

1. A compound represented by the following structural formula:



- 5 or a pharmaceutically acceptable salt thereof, wherein:

L is C₁-C₁₀ alkylene, C₁-C₁₀ alkenylene, or C₁-C₁₀ alkynylene and is

optionally substituted with 1 to 3 groups represented by R₅;

each of X₁, X₃, and X₄ is independently S, O, N, NH or CH and X₂, if

present, is S, O, N, NH or CH, wherein Y₁, if present, is bonded to any

- 10 one of X₁, X₃ and X₄ or X₂, if present, and wherein the X₁, X₃ and X₄ or X₂, if present, to which Y₁ is bonded is C or N;

Y₁ is R₁, R₁-(C₁-C₃)alkylene, R₁-(C₂-C₃)alkenylene, R₁-(C₂-C₃)alkynylene,

R₁-NR₆-, R₁-O-, R₁-S-, R₁-C(O)-, R₁-C(S)-, R₁-SO₂-, R₁-S(O)-, R₁-

C(O)NR₆-, R₁-NR₆C(O)-, R₁-C(O)O-, R₁-OC(O)-, R₁-C(S)NR₆-, R₁-

- 15 NR₆C(S)-, R₁-C(S)O-, R₁-OC(S)-, - R₁-NR₆C(O)NR₆-, R₁-NR₆C(S)NR₆-,
R₁-SO₂NR₆-, R₁-NR₆SO₂-, or R₁-NR₆C(O)O-, wherein the R₁-(C₁-

C₃)alkylene, R₁-(C₂-C₃)alkenylene, or R₁-(C₂-C₃)alkynylene, is

optionally substituted with one to three groups selected from R₅ and

wherein the X₁, X₃ and X₄ or X₂, if present, to which Y₁ is bonded is C;

- 20 R₁ is hydrogen, halogen, -N(R₆)₂, -CN, (C₁-C₆)alkyl, halo(C₁-C₆)alkyl, (C₁-
C₆)alkoxy, (C₁-C₆)alkoxy(C₁-C₆)alkyl, cycloalkyl, aryl, heteroaryl,
heterocyclyl, cycloalkyl(C₁-C₃)alkyl, aryl(C₁-C₃)alkyl, heteroaryl(C₁-
C₃)alkyl, heterocyclyl(C₁-C₃)alkyl, spiro cycloalkyl, or spiro heterocyclyl,
each optionally substituted with one to three groups represented by R₅;

- 25 Y₂ is R_{2a}-(C₁-C₃)alkylene-, R_{2a}-C(O)-, R_{2a}-SO₂-, R_{2a}-S(O)-, R_{2a}-C(O)NR₆-,
R_{2a}-SO₂NR₆-, R_{2a}-R₆C(O)-, or R_{2a}-NR₆SO₂-, wherein the R_{2a}-(C₁-

C₃)alkylene is optionally substituted with one to three groups selected from R₅; or

Y₂ is R_{2b}-;

5 R_{2a} is hydrogen, halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)alkoxy(C₁-C₆)alkyl, cycloalkyl, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclyl, cycloalkyl(C₁-C₃)alkyl, aryl(C₁-C₃)alkyl, heteroaryl(C₁-C₃)alkyl, heterocyclyl(C₁-C₃)alkyl, spiro cycloalkyl, or spiro heterocyclyl, each optionally substituted with one to three groups represented by R₅ or further selected from -N₃, aryloxy, aroyl, benzoate, tert-butyldimethylsiloxy, cylcoalkoxy, heterocycliloxy, or heteroaryl;

10 R_{2b} is hydrogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy(C₁-C₆)alkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(C₁-C₃)alkyl, aryl(C₁-C₃)alkyl, heteroaryl(C₁-C₃)alkyl, heterocyclyl(C₁-C₃)alkyl, spiro cycloalkyl, or spiro heterocyclyl, each optionally substituted with one to three groups represented by R₅ or further selected from -N₃, aryloxy, aroyl, benzoate, tert-butyldimethylsiloxy, cylcoalkoxy, heterocycliloxy, or heteroaryl;

15 Y₃ is R₃-, R₃-(C₁-C₃)alkylene, R₃-C(O)O-, R₃-OC(O)-, R₃-C(O)-, R₃-SO₂-, R₃-SO-, R₃-C(O)NR₆-, R₃-NR₆CO-, R₃-SO₂NR₆, or R₃-NR₆SO₂-, wherein the R₃-(C₁-C₃)alkylene is optionally substituted with R₅;

20 R₃ is hydrogen, halogen, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₁-C₆)alkoxy, (C₁-C₆)alkoxy(C₁-C₆)alkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(C₁-C₃)alkyl, aryl(C₁-C₃)alkyl, heteroaryl(C₁-C₃)alkyl, heterocyclyl(C₁-C₃)alkyl, spiro cycloalkyl, or spiro heterocyclyl, each optionally substituted with one to three groups represented by R₅;

25 R₄ is hydrogen or (C₁-C₆)alkyl optionally substituted with one to three groups represented by R₅; or

30 R₄ and R₃, taken together, form a 5- to 7-membered heterocyclyl, heteroaryl, or spiro heterocyclyl, wherein each ring of the spiro heterocyclyl independently includes 3 to 7 atoms including Y₃ and the nitrogen atom to which R₄ is attached and is optionally substituted with 1 to 3 groups represented by R₅;

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V and W are each independently selected from $-\text{NR}_6-$, $-\text{C}(\text{R}_6)_2-$, $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})-$, and $-\text{S}(\text{O})_2-$;

each R_5 is independently selected from halogen, nitro, cyano, isocyano, hydroxy, (C_1-C_4) alkyl, (C_3-C_6) cycloalkyl, halo (C_1-C_4) alkyl, hydroxy (C_1-C_4) alkyl, (C_1-C_4) alkoxy, (C_1-C_4) alkoxy (C_1-C_4) alkyl, $\text{H}(\text{CH}_2\text{CH}_2\text{O})_m-$, $\text{H}(\text{CH}_2\text{OCH}_2\text{O})_m-$, $\text{H}(\text{CH}_2\text{O})_m-$, $\text{H}(\text{CH}_2\text{OCH}_2\text{CH}_2\text{O})_n-$, $\text{H}(\text{CH}_2\text{CH}_2\text{OCH}_2\text{O})_n-$, $\text{H}(\text{OCH}_2\text{OCH}_2\text{CH}_2)_n-$, $\text{H}(\text{OCH}_2\text{CH}_2\text{OCH}_2)_n-$, $\text{H}(\text{CH}_2\text{OCH}_2\text{CH}_2\text{OCH}_2\text{O})_n-$, $\text{H}(\text{CH}_2\text{OCH}_2)-$, halo (C_1-C_4) alkoxy, aryl, aryloxy, $\text{N}(\text{R}_6)_2$, $-\text{CO}_2\text{R}_6$, $-\text{OCOR}_6$, $-\text{NR}_6\text{CO}_2\text{R}_6$, $-\text{NR}_6\text{CO}_2\text{NR}_6$, $-\text{SO}_2\text{R}_6$, $-\text{SOR}_6$, $-\text{SO}_3\text{R}_6$, $-\text{NR}_6\text{SO}_2\text{R}_6$, $-\text{SO}_2\text{N}(\text{R}_6)_2$, morpholino, piperadyl, and piperazyl;

each R_6 is independently selected from hydrogen or (C_1-C_4) alkyl;

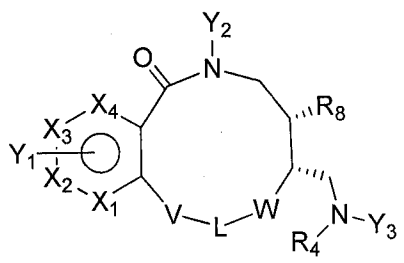
R_8 is hydrogen or (C_1-C_4) alkyl;

m is 1, 2, 3, 4, 5, or 6; and

n is 1, 2, or 3,

provided that Y_2 is not $-\text{CH}(\text{CH}_3)\text{CH}_2\text{OH}$.

2. The compound of Claim 1, wherein the compound is represented by the following structural formula:



or a pharmaceutically acceptable salt thereof.

3. The compound of Claim 1, wherein:

Y_2 is $\text{R}_{2a}-\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_3)-$; or

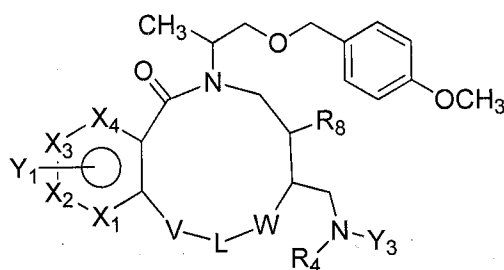
Y_2 is $\text{R}_{2b}-$;

R_{2a} is (C_1-C_6) alkoxy, aryloxy, or heteroaryloxy, each optionally substituted with one to three groups represented by R_5 ;

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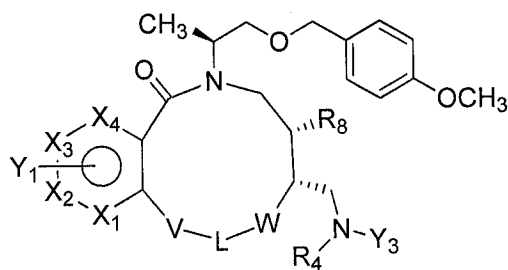
R_{2b} - is $CH_3CH_2CH(CH_3)$ - and is optionally substituted with one group represented by R_5 or further selected from benzoate, tert-butyltrimethylsiloxy, or heterocycloxy; and each R_5 is independently selected from (C_1-C_4) alkoxy, $H(CH_2CH_2O)_m$ -, $H(CH_2OCH_2O)_m$ -, $H(CH_2O)_m$ -, $H(CH_2OCH_2CH_2O)_n$ -, $H(CH_2CH_2OCH_2O)_n$ -, $H(OCH_2OCH_2CH_2)_n$ -, $H(OCH_2CH_2OCH_2)_n$ -, $H(CH_2OCH_2CH_2OCH_2O)_n$ -, $H(CH_2OCH_2)$ -, aryl and aryloxy.

4. The compound of Claim 1, wherein the compound is represented by the following structural formula:



or a pharmaceutically acceptable salt thereof.

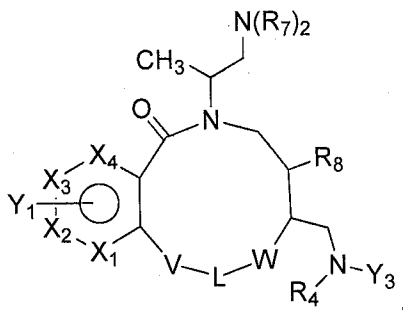
5. The compound of Claim 1, wherein the compound is represented by the following structural formula:



or a pharmaceutically acceptable salt thereof.

6. The compound of Claim 4, wherein the compound is selected from the group consisting of Compounds 1-4, 6-13, 15A, 15B, 16-22, 24-33, 35, 38, 40-44, 49, 50 and 134, or a pharmaceutically acceptable salt thereof.

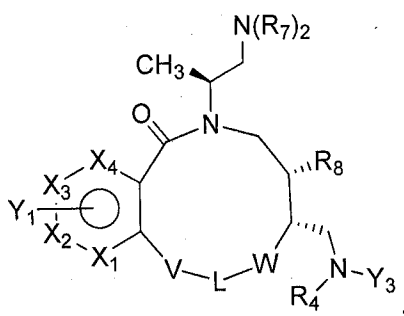
7. The compound of Claim 1, wherein the compound is represented by the following structural formula:



or a pharmaceutically acceptable salt thereof, wherein:

- 5 each R₇ is independently (C₁-C₄)alkyl.

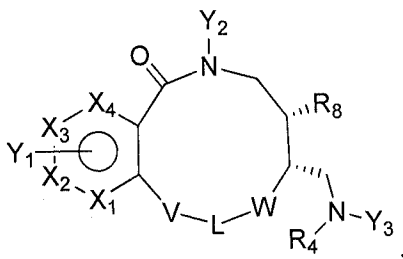
8. The compound of Claim 7, wherein the compound is represented by the following structural formula:



10 or a pharmaceutically acceptable salt thereof.

9. The compound of Claim 7, wherein the compound is selected from the group consisting of Compounds 100-105, ZZ and 111, or a pharmaceutically acceptable salt thereof.

10. A compound represented by the following structural formula:



or a pharmaceutically acceptable salt thereof, wherein:

L is C₁-C₁₀ alkylene, C₁-C₁₀ alkenylene, or C₁-C₁₀ alkynylene and is

optionally substituted with 1 to 3 groups represented by R₅;

each of X₁, X₃, and X₄ is independently S, O, N, NH or CH and X₂, if

5 present, is S, O, N, NH or CH, wherein Y₁, if present, is bonded to any one of X₁, X₃ and X₄ or X₂, if present, and wherein the X₁, X₃ and X₄ or X₂, if present, to which Y₁ is bonded is C or N;

Y₁ is R₁, R₁-(C₁-C₃)alkylene, R₁-(C₂-C₃)alkenylene, R₁-(C₂-C₃)alkynylene,

10 R₁-NR₆-, R₁-O-, R₁-S-, R₁-C(O)-, R₁-C(S)-, R₁-SO₂-, R₁-S(O)-, R₁-C(O)NR₆-, R₁-NR₆C(O)-, R₁-C(O)O-, R₁-OC(O)-, R₁-C(S)NR₆-, R₁-NR₆C(S)-, R₁-C(S)O-, R₁-OC(S)-, -R₁-NR₆C(O)NR₆-, R₁-NR₆C(S)NR₆-, R₁-SO₂NR₆-, R₁-NR₆SO₂-, or R₁-NR₆C(O)O-, wherein the R₁-(C₁-C₃)alkylene, R₁-(C₂-C₃)alkenylene, or R₁-(C₂-C₃)alkynylene, is optionally substituted with one to three groups selected from R₅;

15 R₁ is hydrogen, halogen, -N(R₆)₂, -CN, (C₁-C₆)alkyl, halo(C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)alkoxy(C₁-C₆)alkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(C₁-C₃)alkyl, aryl(C₁-C₃)alkyl, heteroaryl(C₁-C₃)alkyl, heterocyclyl(C₁-C₃)alkyl, spiro cycloalkyl, or spiro heterocyclyl, each optionally substituted with one to three groups represented by R₅;

20 Y₂ is R_{2a}-(C₁-C₃)alkylene-, R_{2a}-C(O)-, R_{2a}-SO₂-, R_{2a}-S(O)-, R_{2a}-C(O)NR₆-, R_{2a}-SO₂NR₆-, R_{2a}-R₆C(O)-, or R_{2a}-NR₆SO₂-, wherein the R_{2a}-(C₁-C₃)alkylene is optionally substituted with one to three groups selected from R₅; or

Y₂ is R_{2b}-;

25 R_{2a} is hydrogen, halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)alkoxy(C₁-C₆)alkyl, cycloalkyl, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclyl, cycloalkyl(C₁-C₃)alkyl, aryl(C₁-C₃)alkyl, heteroaryl(C₁-C₃)alkyl, heterocyclyl(C₁-C₃)alkyl, spiro cycloalkyl, or spiro heterocyclyl, each optionally substituted with one to three groups represented by R₅ or further selected from -N₃, aryloxy, aroyl, benzoate, 30 tert-butyldimethylsiloxy, cycloalkoxy, heterocycliloxy, or heteroaryl;

- R_{2b} is hydrogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy(C₁-C₆)alkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(C₁-C₃)alkyl, aryl(C₁-C₃)alkyl, heteroaryl(C₁-C₃)alkyl, heterocyclyl(C₁-C₃)alkyl, spiro cycloalkyl, or spiro heterocyclyl, each optionally substituted with one to three groups represented by R₅ or further selected from -N₃, aryloxy, aroyl, benzoate, tert-butyldimethylsiloxy, cycloalkoxy, heterocyclyloxy, or heteroaryl;
- Y₃ is R₃-, R₃-(C₁-C₃)alkylene, R₃-C(O)O-, R₃-OC(O)-, R₃-C(O)-, R₃-SO₂-, R₃-SO-, R₃-C(O)NR₆-, R₃-NR₆CO-, R₃-SO₂NR₆, or R₃-NR₆SO₂-, wherein the R₃-(C₁-C₃)alkylene is optionally substituted with R₅;
- R₃ is hydrogen, halogen, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₁-C₆)alkoxy, (C₁-C₆)alkoxy(C₁-C₆)alkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(C₁-C₃)alkyl, aryl(C₁-C₃)alkyl, heteroaryl(C₁-C₃)alkyl, heterocyclyl(C₁-C₃)alkyl, spiro cycloalkyl, or spiro heterocyclyl, each optionally substituted with one to three groups represented by R₅;
- R₄ is hydrogen or (C₁-C₆)alkyl optionally substituted with one to three groups represented by R₅; or
- R₄ and R₃, taken together, form a 5- to 7-membered heterocyclyl, heteroaryl, or spiro heterocyclyl, wherein each ring of the spiro heterocyclyl independently includes 3 to 7 atoms including Y₃ and the nitrogen atom to which R₄ is attached and is optionally substituted with 1 to 3 groups represented by R₅;
- V and W are each independently selected from -NR₆-, -C(R₆)₂-, -O-, -S-, -S(O)-, and -S(O)₂-;
- each R₅ is independently selected from halogen, nitro, cyano, isocyano, hydroxy, (C₁-C₄)alkyl, (C₃-C₆)cycloalkyl, halo(C₁-C₄)alkyl, hydroxy(C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, H(CH₂CH₂O)_m-, H(CH₂OCH₂O)_m-, H(CH₂O)_m-, H(CH₂OCH₂CH₂O)_n-, H(CH₂CH₂OCH₂O)_n-, H(OCH₂OCH₂CH₂)_n-, H(OCH₂CH₂OCH₂)_n-, H(CH₂OCH₂CH₂OCH₂O)_n-, H(CH₂OCH₂)-, halo(C₁-C₄)alkoxy, aryl, aryloxy, N(R₆)₂, -CO₂R₆, -OCOR₆, -NR₆CO₂R₆, -NR₆CO₂NR₆, -SO₂R₆,

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-SOR₆, -SO₃R₆, -NR₆SO₂R₆, -SO₂N(R₆)₂, morpholino, piperadyl, and piperazyl;

each R₆ is independently selected from hydrogen or (C₁-C₄)alkyl;

R₈ is hydrogen or (C₁-C₄)alkyl;

5 m is 1, 2, 3, 4, 5, or 6; and

n is 1, 2, or 3,

wherein if X₁, X₂ and X₄ are each CH, X₃ is C and Y₁ is R₁-NHC(O)NH- and is bonded to X₃, then R₁ is not unsubstituted phenyl.

10 11. The compound of Claim 1 or Claim 10, wherein:

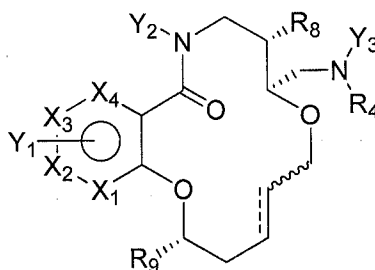
V is O or NR₆;

W is O; and

L is C₁-C₅ alkylene or C₁-C₅ alkenylene and is optionally substituted with methyl.

15

12. The compound of Claim 1 or Claim 10, wherein the compound is represented by the following structural formula:



or a pharmaceutically acceptable salt thereof, wherein:

20 == represents a single or a double bond; and

R₉ is hydrogen or (C₁-C₄)alkyl.

13. The compound of Claim 1 or Claim 10, wherein L is unsubstituted C₂-C₅ alkylene.

25

14. The compound of Claim 1 or Claim 10, wherein X₁, X₂, X₃ and X₄ are each CH.

15. The compound of Claim 1 or 10, wherein X_2 and X_3 are each CH.
16. The compound of Claim 15, wherein X_1 and X_4 are each N.
- 5 17. The compound of Claim 15, wherein X_1 is N and X_4 is CH.
18. The compound of Claim 15, wherein X_1 is CH and X_4 is N.
- 10 19. The compound of Claim 1 or Claim 10, wherein X_2 is absent.
20. The compound of Claim 19, wherein X_4 is S and X_1 and X_3 are each CH.
21. The compound of Claim 19, wherein X_1 is N or NH, X_3 is N or NH, and X_4 is CH.
- 15 22. The compound of Claim 1 or Claim 10, wherein Y_1 is R_1 , $R_1\text{-CH}_2\text{-}$, $R_1\text{-NR}_6\text{-}$, $R_1\text{-C(O)NR}_6\text{-}$, $R\text{-C(O)O-}$, $R_1\text{-NR}_6\text{C(O)NR}_6\text{-}$, or $R_1\text{-SO}_2\text{NR}_6\text{-}$.
- 20 23. The compound of Claim 22, wherein R_1 is hydrogen, halogen, $\text{-N(R}_6)_2$, -CN , $(\text{C}_1\text{-C}_6)\text{alkyl}$, $\text{halo(C}_1\text{-C}_6)\text{alkyl}$, cycloalkyl , aryl or heteroaryl , each optionally substituted with one to three groups represented by R_5 .
24. The compound of Claim 1 or Claim 10, wherein R_{2a} and R_{2b} are each optionally substituted with one to three groups represented by R_5 or further selected from -N_3 , pyridinoxy , benzoxo , p-methoxybenzoxo , benzoate , heterocycloxy , $\text{tert-butyldimethylsiloxy}$, or heteroaryl .
- 25 25. The compound of Claim 1 or Claim 10, wherein Y_3 is R_3 , $R_3\text{-CH}_2\text{-}$, $R_3\text{-C(O)O-}$, $R_3\text{-C(O)-}$, $R_3\text{-SO}_2\text{-}$, or $R_3\text{-C(O)NR}_6\text{-}$.
- 30

26. The compound of Claim 25, wherein R_3 is hydrogen, (C_1-C_6) alkyl, (C_1-C_6) alkenyl, (C_1-C_6) alkoxy, (C_1-C_6) alkoxy (C_1-C_6) alkyl, (C_3-C_7) cycloalkyl, phenyl, or heteroaryl, each optionally substituted with one to three groups represented by R_5 .

5

27. The compound of Claim 1 or Claim 10, wherein R_4 is hydrogen, methyl, ethyl, propyl, isopropyl, butyl or tert-butyl.

28. The compound of Claim 27, wherein R_4 is hydrogen or methyl.

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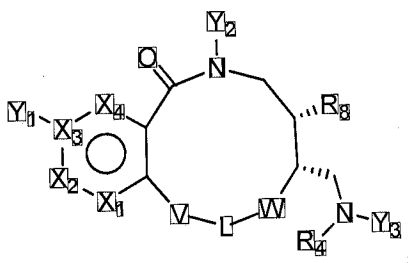
29. The compound of Claim 1 or Claim 10, wherein R_5 is selected from fluoro, chloro, cyano, hydroxy, (C_1-C_4) alkyl, halo (C_1-C_4) alkyl, hydroxy (C_1-C_4) alkyl, (C_1-C_4) alkoxy, $H(CH_2OCH_2CH_2OCH_2O)_n$ -, $H(CH_2OCH_2)$ -, $-NH_2$, $-N(CH_3)_2$, $-NHCH_3$, $-CO_2R_6$, $-NR_6CO_2R_6$, $-NR_6CO_2NR_6$, $-SO_2R_6$, $-NR_6SO_2R_6$, and $-SO_2N(R_6)_2$.

15

30. The compound of Claim 1 or Claim 10, wherein R_8 is hydrogen or methyl.

31. The compound of Claim 1 or Claim 10, wherein the compound is represented by the following structural formula:

20



or a pharmaceutically acceptable salt thereof.

32. The compound of Claim 31, wherein:

25 Y_1 is R_1 , R_1CH_2 -, $R_1-C(O)NR_6$ -, $R_1C(O)O$ -, $R_1-NR_6C(O)NR_6$ - or $R_1SO_2NR_6$ -;

R_1 is hydrogen, halogen, $N(R_6)_2$ -, -CN, (C_1-C_6) alkyl, halo (C_1-C_6) alkyl, cycloalkyl, aryl, or heteroaryl, each optionally substituted with one to three groups represented by R_5 .

Y_2 is R_{2b} or Y_2 is $R_{2a}-(C_1-C_2)$ alkylene-;

5 R_{2a} is (C_1-C_6) alkyl, (C_1-C_6) alkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, or heteroaryl (C_1-C_3) alkyl, each optionally substituted with one to three groups represented by R_5 or further selected from - N_3 , aryloxy, aroyl, benzoate, tert-butyldimethylsiloxy, cylcoalkyloxy, heterocyclyloxy, or heteroaryl;

10 R_{2b} is hydrogen, (C_1-C_6) alkyl, aryl or heteroaryl, each optionally substituted with one to three groups represented by R_5 or further selected from - N_3 , aryloxy, aroyl, benzoate, tert-butyldimethylsiloxy, cylcoalkyloxy, heterocyclyloxy, or heteroaryl;

Y_3 is R_3 -, - CH_2 -, - $C(O)O$ -, - $C(O)$ -, - SO_2 -, or - $C(O)NR_6$ -;

15 R_3 is hydrogen, (C_1-C_6) alkyl, (C_2-C_6) alkenyl, (C_1-C_6) alkoxy, (C_1-C_6) alkoxy (C_1-C_6) alkyl, (C_3-C_7) cycloalkyl, phenyl, or heteroaryl, each optionally substituted with one to three groups represented by R_5 ;

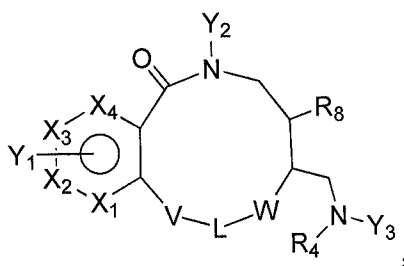
R_4 is hydrogen, methyl, ethyl, propyl, isopropyl, butyl, or tert-butyl; and each R_5 is independently selected from fluoro, chloro, cyano, hydroxy, $(C_1-$

20 $C_4)$ alkyl, halo (C_1-C_4) alkyl, hydroxy (C_1-C_4) alkyl, (C_1-C_4) alkoxy, $H(CH_2OCH_2CH_2OCH_2O)_n$ -, $H(CH_2OCH_2)$ -, $H(CH_2OCH_2O)$ -, NH_2 , $N(CH_3)_2$, $NHCH_3$, - CO_2R_6 , - $NR_6CO_2R_6$, - $NR_6CO_2NR_6$, - SO_2R_6 , - $NR_6SO_2R_6$, and - $SO_2N(R_6)_2$.

25 33. The compound of Claim 31, wherein Y_1 is R_1 , R_1-NH -, $R_1-NHC(O)NH$ -, $R_1-C(O)NH$ -, or R_1-SO_2NH -.

34. The compound of Claim 32, wherein R_1 is hydrogen, fluoro, - CF_3 , NH_2 , -CN, (C_1-C_3) alkyl, phenyl, isoxazoyl, benzoxazoyl, imidazolyl, pyridine, or
30 thiophene, each optionally substituted with one to three groups represented by R_5 .

35. The compound of Claim 31, wherein Y_2 is R_{2b} .
36. The compound of Claim 35, wherein R_{2b} is ethyl or 1-methylethyl,
 5 optionally substituted with p-methoxybenzoxo, (C_1-C_4) alkoxy, hydroxy, or dimethylamino.
37. The compound of Claim 1 or Claim 10, wherein Y_3 is R_3SO_2 .
- 10 38. The compound of Claim 37, wherein R_3 is phenyl optionally substituted with fluoro, chloro, methyl, methoxy, trifluoromethyl, or carboxy.
39. The compound of Claim 1 or Claim 10, wherein R_4 is hydrogen or methyl.
- 15 40. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and a compound of any one of Claims 1-39.
41. A method of treating malaria in a subject in need thereof, comprising administering to the subject an effective amount of a compound represented
 20 by the following structural formula:



or a pharmaceutically acceptable salt thereof, wherein:

L is C_1-C_{10} alkylene, C_1-C_{10} alkenylene, or C_1-C_{10} alkynylene and is optionally substituted with 1 to 3 groups represented by R_5 ;

25 each of X_1 , X_3 , and X_4 is independently S, O, N, NH or CH and X_2 , if present, is S, O, N, NH or CH, wherein Y_1 , if present, is bonded to any

one of X_1 , X_3 and X_4 or X_2 , if present, and wherein the X_1 , X_3 and X_4 or X_2 , if present, to which Y_1 is bonded is C or N;

Y_1 is R_1 , R_1 -(C₁-C₃)alkylene, R_1 -(C₂-C₃)alkenylene, R_1 -(C₂-C₃)alkynylene, R_1 -NR₆-, R_1 -O-, R_1 -S-, R_1 -C(O)-, R_1 -C(S)-, R_1 -SO₂-, R_1 -S(O)-, R_1 -C(O)NR₆-, R_1 -NR₆C(O)-, R_1 -C(O)O-, R_1 -OC(O)-, R_1 -C(S)NR₆-, R_1 -NR₆C(S)-, R_1 -C(S)O-, R_1 -OC(S)-, - R_1 -NR₆C(O)NR₆-, R_1 -NR₆C(S)NR₆-, R_1 -SO₂NR₆-, R_1 -NR₆SO₂-, or R_1 -NR₆C(O)O-, wherein the R_1 -(C₁-C₃)alkylene, R_1 -(C₂-C₃)alkenylene, or R_1 -(C₂-C₃)alkynylene, is optionally substituted with one to three groups selected from R_5 and wherein the X_1 , X_3 and X_4 or X_2 , if present, to which Y_1 is bonded is C;

R_1 is hydrogen, halogen, -N(R₆)₂, -CN, (C₁-C₆)alkyl, halo(C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)alkoxy(C₁-C₆)alkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(C₁-C₃)alkyl, aryl(C₁-C₃)alkyl, heteroaryl(C₁-C₃)alkyl, heterocyclyl(C₁-C₃)alkyl, spiro cycloalkyl, or spiro heterocyclyl, each optionally substituted with one to three groups represented by R_5 ;

Y_2 is R_{2a} -(C₁-C₃)alkylene-, R_{2a} -C(O)-, R_{2a} -SO₂-, R_{2a} -S(O)-, R_{2a} -C(O)NR₆-, R_{2a} -SO₂NR₆-, R_{2a} -R₆C(O)-, or R_{2a} -NR₆SO₂-, wherein the R_{2a} -(C₁-C₃)alkylene is optionally substituted with one to three groups selected from R_5 ; or

Y_2 is R_{2b} -;

R_{2a} is hydrogen, halogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)alkoxy(C₁-C₆)alkyl, cycloalkyl, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclyl, cycloalkyl(C₁-C₃)alkyl, aryl(C₁-C₃)alkyl, heteroaryl(C₁-C₃)alkyl, heterocyclyl(C₁-C₃)alkyl, spiro cycloalkyl, or spiro heterocyclyl, each optionally substituted with one to three groups represented by R_5 or further selected from -N₃, aryloxy, aroyl, benzoate, tert-butyldimethylsiloxy, cycloalkoxy, heterocycliloxy, or heteroaryl;

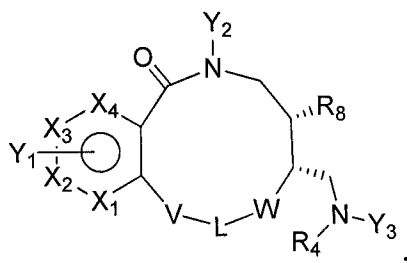
R_{2b} is hydrogen, (C₁-C₆)alkyl, (C₁-C₆)alkoxy(C₁-C₆)alkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(C₁-C₃)alkyl, aryl(C₁-C₃)alkyl, heteroaryl(C₁-C₃)alkyl, heterocyclyl(C₁-C₃)alkyl, spiro cycloalkyl, or spiro heterocyclyl, each optionally substituted with one to three groups

- represented by R_5 or further selected from $-N_3$, aryloxy, aroyl, benzoate, tert-butyldimethylsiloxy, cycloalkoxy, heterocycloxy, or heteroaryl;
- Y_3 is R_3 -, R_3 -(C_1 - C_3)alkylene, R_3 -C(O)O-, R_3 -OC(O)-, R_3 -C(O)-, R_3 -SO₂-, R_3 -SO-, R_3 -C(O)NR₆-, R_3 -NR₆CO-, R_3 -SO₂NR₆-, or R_3 -NR₆SO₂-,
- 5 wherein the R_3 -(C_1 - C_3)alkylene is optionally substituted with R_5 ;
- R_3 is hydrogen, halogen, (C_1 - C_6)alkyl, (C_2 - C_6)alkenyl, (C_2 - C_6)alkynyl, (C_1 - C_6)alkoxy, (C_1 - C_6)alkoxy(C_1 - C_6)alkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(C_1 - C_3)alkyl, aryl(C_1 - C_3)alkyl, heteroaryl(C_1 - C_3)alkyl, heterocyclyl(C_1 - C_3)alkyl, spiro cycloalkyl, or spiro heterocyclyl,
- 10 each optionally substituted with one to three groups represented by R_5 ;
- R_4 is hydrogen or (C_1 - C_6)alkyl optionally substituted with one to three groups represented by R_5 ; or
- R_4 and R_3 , taken together, form a 5- to 7-membered heterocyclyl, heteroaryl, or spiro heterocyclyl, wherein each ring of the spiro heterocyclyl
- 15 independently includes 3 to 7 atoms including Y_3 and the nitrogen atom to which R_4 is attached and is optionally substituted with 1 to 3 groups represented by R_5 ;
- V and W are each independently selected from $-NR_6$ -, $-C(R_6)_2$ -, $-O$ -, $-S$ -, $-S(O)$ -, and $-S(O)_2$;
- 20 each R_5 is independently selected from halogen, nitro, cyano, isocyano, hydroxy, (C_1 - C_4)alkyl, (C_3 - C_6)cycloalkyl, halo(C_1 - C_4)alkyl, hydroxy(C_1 - C_4)alkyl, (C_1 - C_4)alkoxy, (C_1 - C_4)alkoxy(C_1 - C_4)alkyl, $H(CH_2CH_2O)_m$ -, $H(CH_2OCH_2O)_m$ -, $H(CH_2O)_m$ -, $H(CH_2OCH_2CH_2O)_n$ -, $H(CH_2CH_2OCH_2O)_n$ -, $H(OCH_2OCH_2CH_2)_n$ -, $H(OCH_2CH_2OCH_2)_n$ -, $H(CH_2OCH_2CH_2OCH_2O)_n$ -, $H(CH_2OCH_2)$ -, halo(C_1 - C_4)alkoxy, aryl, aryloxy, $N(R_6)_2$, $-CO_2R_6$, $-OCOR_6$, $-NR_6CO_2R_6$, $-NR_6CO_2NR_6$, $-SO_2R_6$, $-SOR_6$, $-SO_3R_6$, $-NR_6SO_2R_6$, $-SO_2N(R_6)_2$, morpholino, piperadyl, and piperazyl;
- 25 each R_6 is independently selected from hydrogen or (C_1 - C_4)alkyl;
- 30 R_8 is hydrogen or (C_1 - C_4)alkyl;
- m is 1, 2, 3, 4, 5, or 6; and

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n is 1, 2, or 3.

42. The method of Claim 41, wherein the compound is represented by the following structural formula:



5

or a pharmaceutically acceptable salt thereof.