

HUMBERTO RUBIO & CIA.

ABOGADOS

Cra. 7 # 74 – 64 Oficina 506
Tel: (571) 3132408 – 3132423 - 3132410 - 3131759
Fax: (571) 3131647 - 3132367
E-mail: mail@rubiolawyers.com
Apartado Aéreo 21848
Bogota, D.C. -Colombia

Doctor

JOSE LUIS SALAZAR LOPEZ

Director de Nuevas Creaciones

Superintendencia de Industria y Comercio

E. S. D.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 11-131281- -00006-0000

Fecha: 2013-07-10 13:57:04 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 523 RESPUESTA Folios: 17

REF: Expediente No. **11-131281**
Patente de Invención: **"HIDRATOS DE INHIBIDORES CÍCLICOS
DE 11BETA-HIDROXIESTEROIDE
DEHIDROGENASA 1".**
Solicitud Internacional No. **PCT/US2010/033157**
Clasificación Internacional: **C07D413/14, A61K31/535,
161P3/00//5/00.**
Titular: **BOEHRINGER INGELHEIM
INTERNATIONAL GmbH
VITAE PHARMACEUTICALS, INC.**

RESPUESTA A REQUERIMIENTO ARTÍCULO 45

OFICIO No. 6568 NOTIFICADO POR ESTADO DE 16 DE ABRIL DE 2013.

HUMBERTO RUBIO CAMACHO, mayor de edad, domiciliado en Bogotá, D.C., identificado con la cédula de ciudadanía número 17'192.062 de Bogotá, abogado graduado portador de la Tarjeta Profesional No. 50.007 expedida por el Consejo Superior de la Judicatura, actuando en carácter de Apoderado de **BOEHRINGER INGELHEIM INTERNATIONAL GmbH**, domiciliada en Binger Strasse 173, 55216 Ingelheim am Rhein, Alemania y **VITAE PHARMACEUTICALS, INC.**, domiciliada en 502 West Office Center Drive, Fort Washington, Pennsylvania 19034, Estados Unidos de America; encontrándome dentro de la debida oportunidad procesal para dar respuesta al auto proferido por su Despacho, mediante Oficio 6568, notificado por fijación en lista 16 de abril de 2013, me permito:

Manifiestar:

I. En el informe emitido sobre la presente invención, se han formulado las objeciones que a continuación resumimos:

a.- Excepción a la Patentabilidad (Art 20 D 486)

El objeto de las reivindicaciones 12-13 y 18-19 no es patentable de acuerdo con el artículo citado.

b. Reivindicaciones relativas a un uso o a un segundo uso (Art 14 y 21 D 486)

El uso de las reivindicaciones 13 - 19 no es patentable, de acuerdo con el Art 14.

c. Título

El título es muy general porque no señala de manera clara el objeto de la invención, es decir los hidratos de los compuestos de la invención. Se solicita hacer la corrección correspondiente.

d. Reivindicaciones (Art 30 D 486, Art 22 PCT)

Las reivindicaciones 1 - 11 no son claras cuando emplean el termino hidrato sin caracterizarse apropiadamente, esto teniendo en cuenta que los hidratos son pseudopolimorfos y su caracterización se hace mediante el patrón de difracción de rayos X en mono cristal, el patrón de difracción de rayos X en polvo (DRXP) con por lo menos los 20 picos correspondientes a las intensidades de los haces difractados o a los espacios interplanares d_{hkl} según los índices de Miller (hkl) medidos de acuerdo con el ángulo de difracción de Bragg 2θ en el intervalo más representativo comprendido entre 5° hasta 90° , las espectroscopias Raman e IR, la espectroscopia RMN- C^{13} , o, los métodos de análisis térmico: TGA, DTA y DSC. Se solicita eliminar el termino o caracterizar el (los) hidrato(s) de acuerdo a lo que se encuentre debidamente soportado en la descripción.

e. Unidad de Invención (Art 25 D 486)

La solicitud no cumple con el requisito de unidad de Invención porque se refiere a 2 grupos inventivos. Los grupos inventivos están definidos por las siguientes características esenciales:

1° Hidratos de los compuestos de fórmula Ip³

2° Hidratos de los compuestos de fórmula Ip¹

La invención frente al problema técnico objetivo de suministrar compuestos que inhiban 11beta-hidroxiesteroide deshidrogenasa 1 (11 β -HSD1) da dos soluciones diferentes. La primera consiste en los hidratos de los compuestos de formula Ip³ y la segunda corresponde a los hidratos de los compuestos de formula Ip¹. Se sugiere presentar las solicitudes divisionales que considere necesarias, o limitar la solicitud inicial a una sola invención, eliminando de ella las otras invenciones.

f. Determinación del Estado de la Técnica

El estado de la técnica se determinó con base en la fecha de presentación de la solicitud de prioridad 30 de abril de 2009 y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

Ítem	Documento	Título	Fecha de Publicación
D1	CO 11 020623	Inhibidores cíclicos de 11 beta -hidroxiesteroide deshidrogenasa 1	20/Diciembre/2011*
D2	CO 10 140916	Inhibidores cíclicos de 11 beta -hidroxiesteroide deshidrogenasa 1	20/Septiembre/2011**

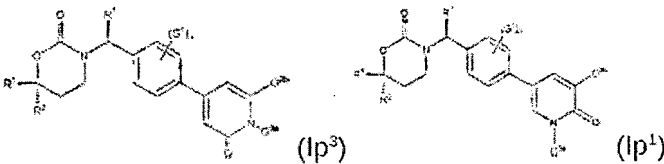
* Publicado en la gaceta 635 de 20 de diciembre de 2011, corresponde a la publicación internacional WO2010/010157, con fecha de prioridad 25/Julio/2008.

** Publicado en la gaceta 632 de 20 de septiembre de 2011, corresponde a la publicación internacional WO2009/134400, con fecha de prioridad 01/Mayo/2008.

g. Examen de Patentabilidad (Art 14 D486)

Novedad (Art 16 D 486)

La reivindicación 1 consiste en un hidrato de un compuesto de fórmula:



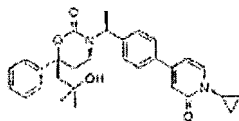
Comparación de las características técnicas esenciales, con las del estado de la técnica:

Características esenciales	D1	D2
Hidrato de un compuesto de fórmula: (Ip ³) (Ip ⁴)	 Ejemplo 48 (Pág. 136) Ejemplo 49 (Pág. 140)	 Ejemplo 48 (Pág. 143) Ejemplo 49 (Pág. 147)
R ¹ es metilo o etilo	Metilo	Metilo
R ² es fenilo o fluorofenilo	Fenilo	Fenilo
R ³ es 2-hidroxi-2-metilpropilo o 2-ciano-2-metilpropilo	2-hidroxi-2-metilpropilo o 2-ciano-2-metilpropilo	2-hidroxi-2-metilpropilo o 2-ciano-2-metilpropilo
G ¹ es alquilo C1-4, haloalquilo C1-4, haloalcoxi C1-4, halógeno, ciano o nitro	No aplica	No aplica
n es 0, 1 o 2	0	0
G ^{2a} es alquilo C1-4, haloalquilo C1-4, cicloalquilo C3-4 o cicloalquil C3-4 alquilo C1-2	Metilo	Metilo
G ^{2b} es hidrógeno, metilo o etilo	Hidrógeno	Hidrógeno

Las características esenciales de los compuestos de la reivindicación 1 habían sido divulgadas previamente en D1 y D2, en consecuencia la reivindicación 1 no es nueva.

Las reivindicaciones dependientes 2, 10 y 11 no mencionan alguna característica que haga nueva a la composición de la reivindicación 1, por lo cual se considera que no son nuevas.

La reivindicación 3 consiste en el hidrato de la reivindicación 1, en el que el compuesto está representado por la siguiente formula estructural:

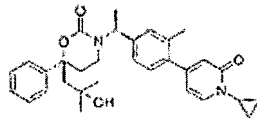


Comparación de las características técnicas esenciales, con las del estado de la técnica:

Características esenciales	D1	D2
Hidrato de un compuesto de fórmula: 	 Ejemplo 75 (Pág. 168)	 Ejemplo 75 (Pág. 160)

Las características esenciales del compuesto de la reivindicación 3 habían sido divulgadas previamente en D1 y D2, en consecuencia la reivindicación 3 no es nueva.

La reivindicación 4 consiste en el hidrato de la reivindicación 1, en el que el compuesto está representado por la siguiente formula estructural:

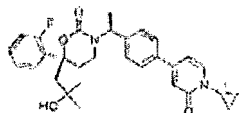


Comparación de las características técnicas esenciales, con las del estado de la técnica:

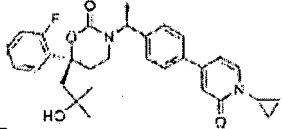
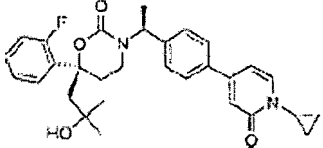
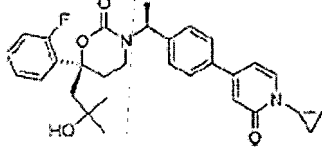
Características esenciales	D1
Hidrato de un compuesto de fórmula: 	 Ejemplo 97 (Pág. 192)

Las características esenciales del compuesto de la reivindicación 4, habían sido divulgadas previamente en D1, en consecuencia, la reivindicación 4 no es nueva.

La reivindicación 5 consiste en el hidrato de la reivindicación 1, en el que el compuesto está representado por la siguiente formula estructural:

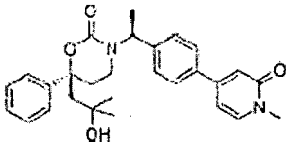


Comparación de las características técnicas esenciales, con las del estado de la técnica:

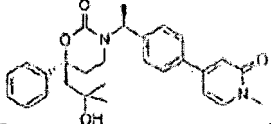
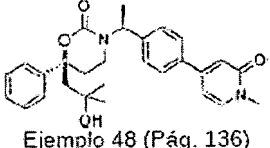
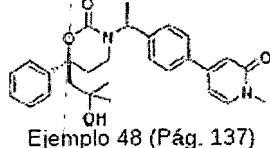
Características esenciales	D1	D2
Hidrato de un compuesto de fórmula: 	 Ejemplo 88 (Pág. 178)	 Ejemplo 88 (Pág. 180)

Las características esenciales del compuesto de la reivindicación 5, habían sido divulgadas previamente en D1 y D2, en consecuencia, la reivindicación 5 no es nueva.

La reivindicación 6 consiste en el hidrato de la reivindicación 1, en el que el compuesto está representado por la siguiente formula estructural:

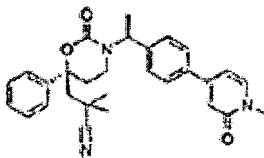


Comparación de las características técnicas esenciales, con las del estado de la técnica:

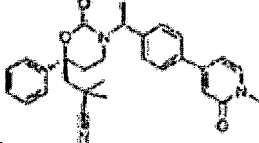
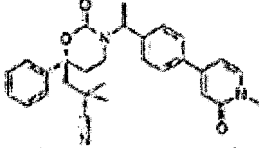
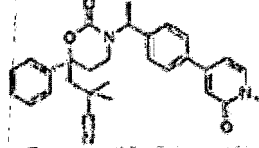
Características esenciales	D1	D2
Hidrato de un compuesto de fórmula: 	 Ejemplo 48 (Pág. 136)	 Ejemplo 48 (Pág. 137)

Las características esenciales del compuesto de la reivindicación 6, habían sido divulgadas previamente en D1 y D2, en consecuencia, la reivindicación 6 no es nueva.

La reivindicación 7 consiste en el hidrato de la reivindicación 1, en el que el compuesto está representado por la siguiente formula estructural:



Comparación de las características técnicas esenciales, con las del estado de la técnica:

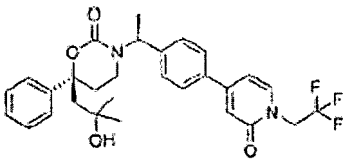
Características esenciales	D1	D2
Hidrato de un compuesto de fórmula: 	 Ejemplo 50 (Pág. 142)	 Ejemplo 50 (Pág. 142)

Las características esenciales del compuesto de la reivindicación 7, habían sido divulgadas previamente en D1 y D2, en consecuencia, la reivindicación 7 no es nueva.

HUMBERTO RUBIO & CIA.

ABOGADOS
Expediente No. 11-131281
Pagina 6 de 10

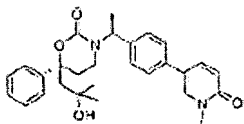
La reivindicación 8 consiste en el hidrato de la reivindicación 1, en el que el compuesto está representado por la siguiente formula estructural:



Comparación de las características técnicas esenciales, con las del estado de la técnica:		
Características esenciales	D1	D2
Hidrato de un compuesto de fórmula: 	 Ejemplo 66 (Pág. 151)	 Ejemplo 66 (Pág. 152)

Las características esenciales del compuesto de la reivindicación 8, habían sido divulgadas previamente en D1 y D2, en consecuencia, la reivindicación 8 no es nueva.

La reivindicación 9 consiste en el hidrato de la reivindicación 1, en el que el compuesto está representado por la siguiente formula estructural:



Comparación de las características técnicas esenciales, con las del estado de la técnica:		
Características esenciales	D1	D2
Hidrato de un compuesto de fórmula: 	 Ejemplo 37 (Pág. 127)	 Ejemplo 37 (Pág. 127)

Las características esenciales del compuesto de la reivindicación 8, habían sido divulgadas previamente en D1 y D2, en consecuencia, la reivindicación 9 no es nueva.

h. Conclusión:

Los requisitos de patentabilidad de la presente solicitud están afectados por D1.

Item	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	CO 11 020623	1 - 11	Novedad
D2	CO 10 140916	1 - 11	Novedad

II.- En contestación a las observaciones anteriores, manifestamos lo siguiente:

Reivindicaciones relativas a un uso o a un segundo uso.

Presentamos junto con esta respuesta un nuevo capítulo reivindicatorio, en el cual se han introducido las siguientes enmiendas:

1. Las reivindicaciones originales 12-13 y 18-19 se han eliminado del mismo, por contener materia no patentable, de conformidad con el Artículo 20, D 486, literal (d).
2. Las reivindicaciones originales 14-17 se han eliminado por corresponder a la categoría de uso, la cual no se considera patentable según el Artículo 14, D 486.
3. El contenido de las reivindicaciones se ha limitado al Grupo Inventivo I señalado en el examen de patentabilidad, es decir a los hidratos de los compuestos que tiene la fórmula (Ip³), con el objetivo acelerar la concesión de la patente. Sin embargo, me reservo el derecho de presentar solicitudes de patentes divisionales para la materia no contenida en el nuevo capítulo reivindicatorio que se adjunta, lo cual está expresamente permitido en el Artículo 36, D 486.
4. Se han incluido además nuevas reivindicaciones que están dirigidas a las formas monohidratadas de compuestos específicos. Estas nuevas reivindicaciones se han aprobado recientemente en la solicitud de patente correspondiente de los Estados Unidos No. 13/318,271, y se encuentran debidamente sustentadas en la descripción de la solicitud original, véase por ejemplo en las páginas 162-174, Ejemplo 48, y en las páginas 197-206, Ejemplo 75, de la publicación de la solicitud internacional.

En relación a las restantes objeciones planteadas en el examen de patentabilidad manifestamos:

De la Solicitud de Patente

Título: Se plantea en el reporte del examen de patentabilidad, que el título es muy general ya que no se señala de manera clara el objeto de la invención, es decir los hidratos de los compuestos de la invención.

Para superar esta objeción, pedimos expresamente cambio del título actual por el de:

“HIDRATOS DE INHIBIDORES CÍCLICOS DE 11BETA-HIDROXIESTEROIDE DEHIDROGENASA 1”.

Reivindicaciones (Artículo 30 D486, Artículo 22 PCT)

Se plantea que las reivindicaciones 1 - 11 no son claras cuando emplean el término hidrato sin caracterizarlos apropiadamente, y en la objeción se mencionan los parámetros técnicos que, en opinión de examinador, deberían utilizarse para caracterizar apropiadamente estos compuestos de conformidad con lo que se encuentra debidamente sustentado en la descripción.

Discrepamos respetuosamente de la objeción anterior, ya que con ella, al parecer el examinador exige que el solicitante presenten datos que caracterizan a todo un género de compuestos de hidratos, lo cual no es en lo absoluto práctico. Es decir, sólo sería posible en un sentido teórico lograr los datos sobre los compuestos citados en forma genérica. Además, un experto en la materia entenderá que un hidrato, por definición, es cualquier compuesto que contiene agua en forma de moléculas de H_2O , lo cual es generalmente, pero no siempre, con un contenido definido de agua en peso. Es decir, no todos los hidratos están presentes en forma cristalina, por lo tanto es imposible caracterizarlos a todos, que se han reivindicados de forma genérica, de conformidad con sus parámetros físico-químicos particulares, como pretende el examinador.

Por todo lo anterior entendemos que las reivindicaciones, tal cual se han redactado, son claras, y por consiguiente, la objeción del examinador debe retirarse. ***

Unidad de Invención

El examinador ha determinado que la solicitud no cumple con el requisito de unidad de Invención porque se refiere a 2 grupos inventivos, los cuales se definen por las siguientes características esenciales:

1. Hidratos de los compuestos de formula lp^3
2. Hidratos de los compuestos de formula lp^1

Si bien discrepamos de esta conclusión del examinador, solo con el ánimo de acelerar la concesión la presente solicitud es que hemos eliminado las reivindicaciones concernientes al segundo grupo inventivo previamente mencionado, materia que será objeto de una solicitud divisional de la actual. En consecuencia de esta enmienda, la objeción acerca de la falta de unidad de invención debe eliminarse.

Examen de Patentabilidad

En el examen del cumplimiento del requisito de Novedad (Art 16 D 486) de la presente solicitud, el examinador concluye que las reivindicaciones 1-11 no son nuevas en virtud de los documentos del Estado de la Técnica D1 (CO 11 020623, correspondiente a la solicitud internacional PCT/EP2009/05950) y D2 (CO 10 140916, correspondiente a la solicitud internacional PCT/US2009/002653).

En primer lugar aclaramos que para que el requerimiento de novedad sea impugnado para una reivindicación independiente, un único documento del estado de la técnica tiene que anticipar todas las características técnicas de dicha reivindicación. Si la combinación de dos documentos anticipa esas características, pues entonces el requisito a impugnar no es novedad sino nivel inventivo.

En el presente caso, respetuosamente discrepamos del criterio del examinador de que los compuestos de la presente solicitud no son nuevos a la luz de los documentos D1 y D2.

Para un análisis certero de la patentabilidad de la presente invención, debe considerarse cuidadosamente la fecha de prioridad de los compuestos reivindicados y de los citados contra su novedad.

La primera divulgación de los compuestos hidratados que tienen la fórmula reivindicada fue en el documento D2, cuya solicitud se presentó el 30/04/2009, para la cual la presente solicitud reivindica su prioridad. Véase los Ejemplos 37, 48 y 75 de D2. Adicionalmente, los Ejemplos 49, 50, 88, y 62 de D2, contrario a lo que menciona el examinador, no se divulgaron en D2 como hidratos. Como se podrá notar, el documento D2 reivindica la prioridad para cuatro solicitudes anteriores, la más reciente de las cuales es la solicitud provisional de Estados Unidos No. 61/206,785, presentada el 4 de febrero del 2009, copia adjunta.

El examinador debe notar que la preparación de los compuestos hidratados representada por los Ejemplos 37, 48 y 75 de D2, no se da a conocer en la solicitud provisional de Estados Unidos No. 61/206,785. Como tal, la materia reivindicada en la presente solicitud tiene derecho a la prioridad de D2. Por lo tanto, D2 no se puede considerar como documento del estado de la técnica relevante para la novedad de la presente invención.

En cuanto a la divulgación de D1, entendemos que esta referencia no puede considerarse como estado de la técnica anterior, ya que la materia reivindicada en la presente solicitud tiene derecho a la prioridad del

HUMBERTO RUBIO & CIA.

ABOGADOS

Expediente No. 11-131281

Pagina 10 de 10

documento D2, y D2 tiene una prioridad anterior a la del documento D1. Por lo tanto, esta referencia tampoco es relevante para la novedad de la presente invención.

Por lo anteriormente expuesto consideramos que la presente solicitud es novedosa, las reivindicaciones, según se han enmendado, definen la materia que se desea proteger dentro de la materias que son aceptadas como patentables según la Decisión 486, siendo claras, concisas y debidamente sustentadas en la descripción original y no están comprendida en el estado de la técnica, conforme lo establece el Art. 14, 16 y 30 de la Decisión 486.

De manera atenta solicito a su Despacho, tener en cuenta todos y cada una de las consideraciones expuestas anteriormente, al momento de estudiar el presente caso.

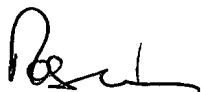
Anexo:

- i. Nuevo capítulo reivindicatorio.
- ii. Copia en CD de la solicitud provisional 61/206,785
- iii. Recibo de pago No. 13-0068223 correspondiente a la reivindicación adicional.

Petición:

Conforme a lo anterior, una vez atendidos los requerimientos y exigencias del examinador y al tener en cuenta el capítulo reivindicatorio modificado que se presenta con la presente contestación, solicito muy respetuosamente a su Despacho, continuar el trámite de rigor y de ser el caso se hagan las correspondientes observaciones con el ánimo de hacer lo pertinente dentro del presente trámite.

Atentamente,



HUMBERTO RUBIO CAMACHO

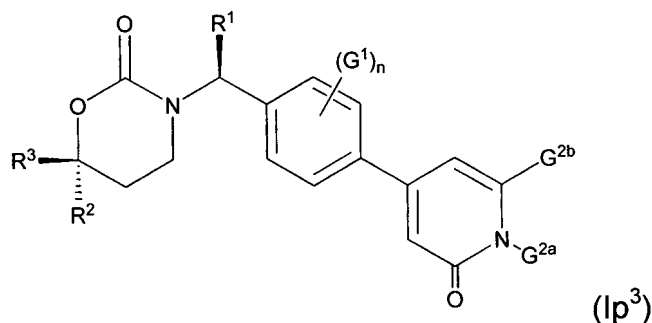
C.C. 17'192.062 de Bogotá

**T.P. 50.007 Consejo Superior
de la Judicatura**

COD. 4134

REIVINDICACIONES

1. Un hidrato de un compuesto representado por la fórmula estructural seleccionada entre:



o una sal farmacéuticamente aceptable del mismo, en la que:

G^1 es alquilo (C_1-C_4), alcoxi (C_1-C_4), haloalquilo (C_1-C_4), haloalcoxi (C_1-C_4), halógeno, ciano o nitro;

n es 0, 1 ó 2;

G^{2a} es alquilo (C_1-C_4), haloalquilo (C_1-C_2), cicloalquilo (C_3-C_4) o cicloalquil (C_3-C_4) alquilo (C_1-C_2);

G^{2b} es hidrógeno, metilo o etilo;

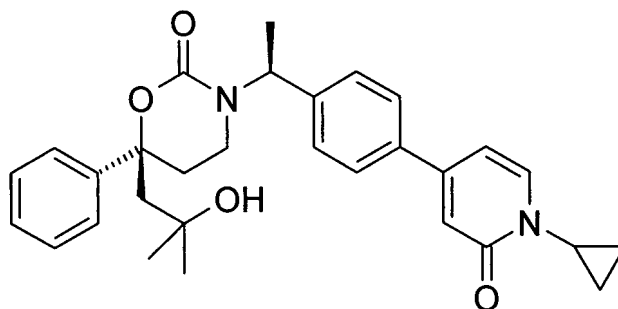
R^1 es metilo o etilo;

R^2 es fenilo o fluorofenilo; y

R^3 es 2-hidroxi-2-metilpropilo o 2-ciano-2-metilpropilo.

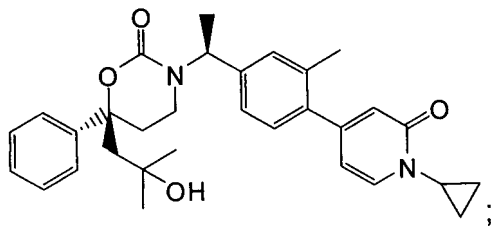
2. El hidrato de la reivindicación 1, en el que n es 0.

3. El hidrato de la reivindicación 1, en el que el compuesto está representado por la siguiente fórmula estructural:



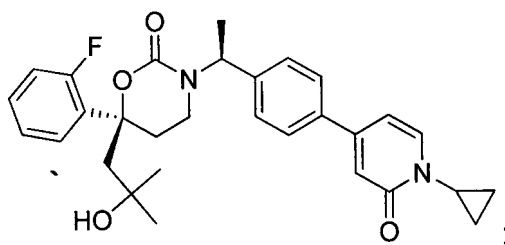
o una sal farmacéuticamente aceptable del mismo.

4. El hidrato de la reivindicación 1, en el que el compuesto está representado por la siguiente fórmula estructural:



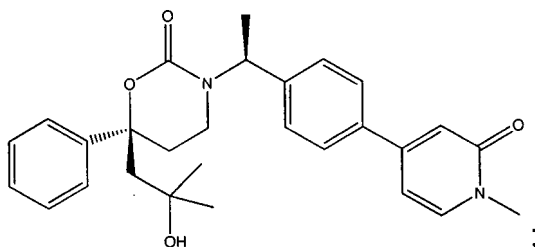
o una sal farmacéuticamente aceptable del mismo.

5. El hidrato de la reivindicación 1, en el que el compuesto está representado por la siguiente fórmula estructural:



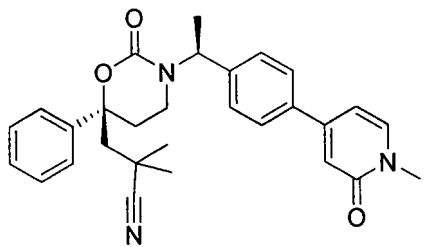
o una sal farmacéuticamente aceptable del mismo.

6. El hidrato de la reivindicación 1, en el que el compuesto está representado por la siguiente fórmula estructural:



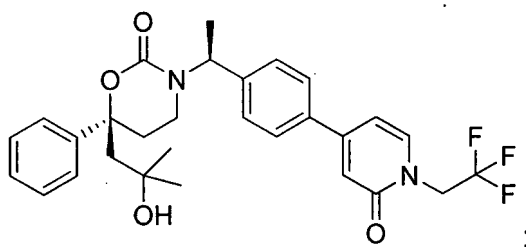
o una sal farmacéuticamente aceptable del mismo.

7. El hidrato de la reivindicación 1, en el que el compuesto está representado por la siguiente fórmula estructural:



o una sal farmacéuticamente aceptable del mismo.

8. El hidrato de la reivindicación 1, en el que el compuesto está representado por la siguiente fórmula estructural:



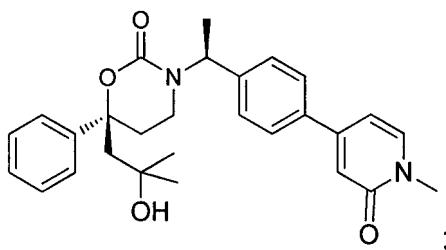
o una sal farmacéuticamente aceptable del mismo.

9. El hidrato de una cualquiera de las reivindicaciones 1-8, en el que el compuesto es un monohidrato.

10. Una composición farmacéutica que comprende:

- i) un vehículo o diluyente farmacéuticamente aceptable; y
- ii) el hidrato de una cualquiera de las reivindicaciones 1-9.

11. Un compuesto representado por la siguiente fórmula estructural:



donde el compuesto es un monohidrato y cristalino.

12. El compuesto de la reivindicación 11, en el que el compuesto cristaliza en el grupo espacial ortorrómbico $P2_12_12_1$.

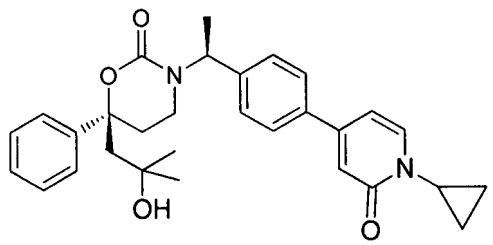
13. El compuesto de la reivindicación 11, en el que el compuesto se caracteriza por picos de difracción de rayos x de polvo a ángulos de 2θ de 8,71, 12,93 y 19,16 grados ($\pm 0,05$ grados) usando radiación $\text{CuK } \alpha_1$.

14. El compuesto de la reivindicación 13, en el que el compuesto se caracteriza por picos de difracción de rayos x de polvo a ángulos de 2θ de 8,71, 12,93, 19,16, 19,45 y 21,06 grados ($\pm 0,05$ grados) usando radiación $\text{CuK } \alpha_1$.

15. Una composición farmacéutica que comprende:

- i) un vehículo o diluyente farmacéuticamente aceptable, y
- ii) el compuesto de la reivindicación 11.

16. Un compuesto representado por la siguiente fórmula estructural:



donde el compuesto es un monohidrato y cristalino.

17. El compuesto de la reivindicación 16, en el que el compuesto cristaliza en el grupo espacial ortorrómbico $P2_12_12_1$.
18. El compuesto de la reivindicación 16, en el que el compuesto se caracteriza por picos de difracción de rayos x de polvo a ángulos de 2θ de 21,00, 21,72, y 23,98 grados ($\pm 0,05$ grados) usando radiación $\text{CuK } \alpha_1$.
19. El compuesto de la reivindicación 18, en el que el compuesto se caracteriza por picos de difracción de rayos x de polvo a ángulos de 2θ de 14,25, 21,00, 21,72, 23,10, 23,98, y 27,04 grados ($\pm 0,05$ grados) usando radiación $\text{CuK } \alpha_1$.
20. Una composición farmacéutica que comprende:
 - i) un vehículo o diluyente farmacéuticamente aceptable, y
 - ii) el compuesto de la reivindicación 16.

Document made available under the Patent Cooperation Treaty (PCT)

International application number: PCT/US2009/002653

International filing date: 30 April 2009 (30.04.2009)

Document type: Certified copy of priority document

Document details: Country/Office: US
Number: 61/206,785
Filing date: 04 February 2009 (04.02.2009)

Date of receipt at the International Bureau: 14 May 2009 (14.05.2009)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)



World Intellectual Property Organization (WIPO) - Geneva, Switzerland
Organisation Mondiale de la Propriété Intellectuelle (OMPI) - Genève, Suisse

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
NIT : 800.176.089-2
- / -

 Industria y Comercio SUPERINTENDENCIA	RECIBO DE CAJA	No. 13 - 0068223
		Bogotá D.C., Julio 10 de 2013 - 10:23:30

RECIBIDO DE : HUMBERTO RUBIO & CIA ABOGADOS LTDA					NI 830.000.228
*** Soporte del Pago ***					
TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR. PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	523144845	10/07/2013	5.455.000.00

*** Conceptos Pagados ***				
CANT.	RENTISTICO	CONCEPTO	Vr. UNDITARIO	Vr. CONCEPTO
1	50005-01-01 SOLICITUDES	1607 REIVINDICACION PATENTE UNITARIA ADICIONAL A LAS 10 INIC	30.000.00	30.000.00
				\$30.000.00
=====				

SON: **TREINTA MIL PESOS MONEDA CORRIENTE**

Responsable: _____

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 11-131281- -00006-0000
Fecha: 2013-07-10 13:57:04 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 523 RESPUESTA Folios: 17

EXCEDENTES DE REIVINDICACIONES
PATENTE: HIDRATOS DE INHIBIDORES CÍCLICOS DE 11BETA-
HIDROXIESTEROIDE DEHIDROGENASA

Document made available under the Patent Cooperation Treaty (PCT)

International application number: PCT/US2009/002653

International filing date: 30 April 2009 (30.04.2009)

Document type: Certified copy of priority document

Document details: Country/Office: US
Number: 61/206,785
Filing date: 04 February 2009 (04.02.2009)

Date of receipt at the International Bureau: 14 May 2009 (14.05.2009)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)



World Intellectual Property Organization (WIPO) - Geneva, Switzerland
Organisation Mondiale de la Propriété Intellectuelle (OMPI) - Genève, Suisse

164961

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

May 13, 2009

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE.

APPLICATION NUMBER: 61/206,785

FILING DATE: *February 04, 2009*

RELATED PCT APPLICATION NUMBER: *PCT/US09/02653*

THE COUNTRY CODE AND NUMBER OF YOUR PRIORITY APPLICATION, TO BE USED FOR FILING ABROAD UNDER THE PARIS CONVENTION, IS *US61/206,785*



Certified by

Under Secretary of Commerce
for Intellectual Property
and Director of the United States
Patent and Trademark Office

020409 17607 U.S. PTO

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR § 1.53(c)

U.S. PTO
61/206785
02/04/2009

Express Mail Label Number **EV 214 932 719 US**

Docket Number **4108.1013-001**

INVENTOR(S)

Given Name (first and middle (if any))	Family Name or Surname	Residence (City and either state or Foreign Country)
David A.	Claremon	Maple Glen, PA

☐ Additional inventors are being named on the separately numbered sheet(s) attached hereto

TITLE OF THE INVENTION (500 characters max)

CYCLIC INHIBITORS OF 11 β -HYDROXYSTEROID DEHYDROGENASE 1

ENCLOSED APPLICATION PARTS (check all that apply)

- ☒ Specification Number of Pages **189** ☐ Other (specify) _____
(May include drawings interspersed throughout)
- ☐ Separate Drawing(s) Number of Sheets []

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT

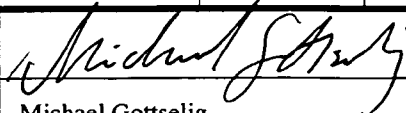
	FILING FEE AMOUNT
☒ Filing Fee	\$ 220
☒ Application Size Fee	
☒ Filed via Express Mail - Combine specification and drawing sheets. \$270 for each add'l 50 sheets over 100	\$ 540
☐ Filed Electronically - Total specification & drawing sheets X .75 (If a fraction remains, add 1 page to the total thereby including the fraction). Using the total after calculation, the fee is \$270 for each additional 50 sheets over 100.	\$
TOTAL OF ABOVE CALCULATIONS	\$ 760
☐ Applicant claims small entity status.	The total fee indicated has been reduced by 1/2 \$ _____
☒ A check is enclosed to cover the filing fees. Please charge any deficiency in fees and credit any overpayment to Deposit Account Number 08-0380 .	
☐ The Director is hereby authorized to charge filing fees or credit any overpayment to Deposit Account Number 08-0380 .	
☐ Previously Submitted.	

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

- ☒ No
- ☐ Yes, the name of the U.S. Government agency and the Government contract number are: _____

CORRESPONDENCE ADDRESS

Direct all correspondence to:

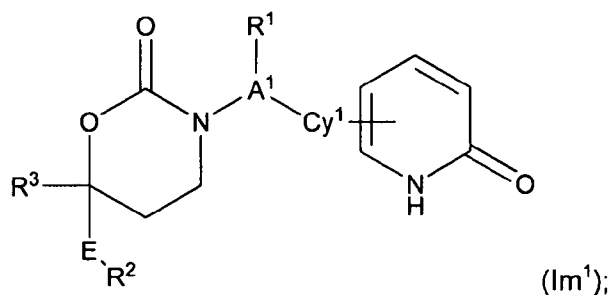
CUSTOMER NO.	021005					
NAME	HAMILTON, BROOK, SMITH & REYNOLDS, P.C.					
ADDRESS	530 Virginia Road, P.O. Box 9133					
CITY	Concord	STATE	MA	ZIP CODE	01742-9133	
COUNTRY	USA	TELEPHONE	(978) 341-0036	FAX	(978) 341-0136	
Signature				Date	Feb. 4, 2009	
Submitted by Typed or Printed Name	Michael Gottselig			Reg. Number	57,941	

CLAIMS

What is claimed is:

5

1. A compound of Formula (Im¹)



10

wherein:

R¹ is (a) absent or (b) is selected from (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₁-C₃)alkoxy(C₁-C₃)alkoxy, or (C₁-C₃)alkoxy(C₁-C₃)alkyl and is optionally substituted with up to four groups independently selected from fluorine, cyano, oxo, R⁴, R⁴O-, (R⁴)₂N-,

- 15 R⁴O₂C-, R⁴S, R⁴S(=O)-, R⁴S(=O)₂-, R⁴C(=O)NR⁴-, (R⁴)₂NC(=O)-, (R⁴)₂NC(=O)O-, (R⁴)₂NC(=O)NR⁴-, R⁴OC(=O)NR⁴-, (R⁴)₂NC(=N)NR⁴-, (R⁴O)₂P(=O)O-, (R⁴O)₂P(=O)NR⁴-, R⁴OS(=O)₂NR⁴-, (R⁴)₂NS(=O)₂O-, (R⁴)₂NS(=O)₂NR⁴-, R⁴S(=O)₂NR⁴-, R⁴S(=O)₂NHC(=O)-, R⁴S(=O)₂NHC(=O)O-, R⁴S(=O)₂NHC(=O)NR⁴-, R⁴OS(=O)₂NHC(=O)-, R⁴OS(=O)₂NHC(=O)O-, R⁴OS(=O)₂NHC(=O)NR⁴-,
- 20 (R⁴)₂NS(=O)₂NHC(=O)-, (R⁴)₂NS(=O)₂NHC(=O)O-, (R⁴)₂NS(=O)₂NHC(=O)NR⁴-, R⁴C(=O)NHS(=O)₂-, R⁴C(=O)NHS(=O)₂O-, R⁴C(=O)NHS(=O)₂NR⁴-, R⁴OC(=O)NHS(=O)₂-, R⁴OC(=O)NHS(=O)₂O-, R⁴OC(=O)NHS(=O)₂NR⁴-, (R⁴)₂NC(=O)NHS(=O)₂-, (R⁴)₂NC(=O)NHS(=O)₂O-, (R⁴)₂NC(=O)NHS(=O)₂NR⁴-, heterocyclyl, heteroaryl, arylamino and heteroarylamino;
- 25 A¹ is (a) a bond, or (b) (C₁-C₃)alkylene, CH₂CH₂O, wherein the oxygen is attached to Cy¹, or CH₂C(=O), wherein the carbonyl carbon is attached to Cy¹;

Cy¹ is aryl, heteroaryl, monocyclic cycloalkyl or monocyclic heterocyclyl and is optionally substituted with 1 to 4 groups independently selected from fluorine, chlorine, bromine, iodine, cyano, nitro, amino, hydroxy, carboxy, (C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, hydroxy(C₃-C₆)cycloalkyl, (C₄-C₇)cycloalkylalkyl, (C₂-C₆)alkenyl, halo(C₂-C₆)alkenyl, hydroxy(C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₆)cycloalkyl(C₂-C₄)alkynyl, halo(C₁-C₆)alkyl, halo(C₃-C₆)cycloalkyl, halo(C₄-C₇)cycloalkylalkyl, (C₁-C₆)alkoxy, (C₃-C₆)cycloalkoxy, (C₄-C₇)cycloalkylalkoxy, halo(C₁-C₆)alkoxy, halo(C₃-C₆)cycloalkoxy, halo(C₄-C₇)cycloalkylalkoxy, (C₁-C₆)alkylthio, (C₃-C₆)cycloalkylthio, (C₄-C₇)cycloalkylalkylthio, halo(C₁-C₆)alkylthio, halo(C₃-C₆)cycloalkylthio, halo(C₄-C₇)cycloalkylalkylthio, (C₁-C₆)alkanesulfinyl, (C₃-C₆)cycloalkanesulfinyl, (C₄-C₇)cycloalkylalkanesulfinyl, halo(C₁-C₆)alkanesulfinyl, halo(C₃-C₆)cycloalkanesulfinyl, halo(C₄-C₇)cycloalkylalkanesulfinyl, (C₁-C₆)alkanesulfonyl, (C₃-C₆)cycloalkanesulfonyl, (C₄-C₇)cycloalkylalkanesulfonyl, halo(C₁-C₆)alkanesulfonyl, halo(C₃-C₆)cycloalkanesulfonyl, halo(C₄-C₇)cycloalkylalkanesulfonyl, (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, (C₁-C₆)alkoxy(C₁-C₆)alkoxy, halo(C₁-C₆)alkoxy(C₁-C₆)alkoxy, (C₁-C₆)alkoxycarbonyl, H₂NCO, H₂NSO₂, (C₁-C₆)alkylaminocarbonyl, di(C₁-C₆)alkylaminocarbonyl, (C₁-C₃)alkoxy(C₁-C₃)alkylaminocarbonyl, heterocyclylcarbonyl, (C₁-C₆)alkylaminosulfonyl, di(C₁-C₆)alkylaminosulfonyl, heterocyclosulfonyl, (C₁-C₆)alkylcarbonylamino, (C₁-C₆)alkylcarbonylamino(C₁-C₆)alkyl, (C₁-C₆)alkylsulfonylamino, (C₁-C₆)alkylsulfonylamino(C₁-C₆)alkyl, (C₁-C₆)alkoxycarbonyl(C₁-C₆)alkoxy, (C₁-C₆)alkoxy(C₁-C₆)alkyl, halo(C₁-C₆)alkoxy(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkoxy, heteroaryl oxo, amino(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)alkyl, di(C₁-C₆)alkylamino(C₁-C₆)alkyl amino(C₂-C₆)alkoxy, (C₁-C₆)alkylamino(C₂-C₆)alkoxy, di(C₁-C₆)alkylamino(C₂-C₆)alkoxy, (C₁-C₆)alkylcarbonyl, (C₃-C₆)cycloalkylcarbonyl, (C₃-C₆)cycloalkylaminocarbonyl, {(C₃-C₆)cycloalkyl}{(C₁-C₆)alkyl}aminocarbonyl, di(C₃-C₆)cycloalkylaminocarbonyl, (C₃-C₆)cycloalkylaminosulfonyl, {(C₃-C₆)cycloalkyl}{(C₁-C₆)alkyl}aminosulfonyl, di(C₃-C₆)cycloalkylaminosulfonyl, cyano(C₁-C₆)alkyl, aminocarbonyl(C₁-C₆)alkyl, (C₁-C₆)alkylaminocarbonyl(C₁-C₆)alkyl, di(C₁-C₆)alkylaminocarbonyl(C₁-C₆)alkyl, (C₃-C₆)cycloalkylaminocarbonyl(C₁-C₆)alkyl, {(C₃-C₆)cycloalkyl}{(C₁-C₆)alkyl}aminocarbonyl(C₁-C₆)alkyl and di(C₃-C₆)cycloalkylaminocarbonyl(C₁-C₆)alkyl;

the oxodihydropyridyl ring in Formula Im¹ is optionally substituted with 1 to 4 groups independently selected from fluorine, chlorine, bromine, iodine, cyano, nitro, amino,

- hydroxy, carboxy, (C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, hydroxy(C₃-C₆)cycloalkyl, (C₄-C₇)cycloalkylalkyl, (C₂-C₆)alkenyl, halo(C₂-C₆)alkenyl, hydroxy(C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₆)cycloalkyl(C₂-C₄)alkynyl, halo(C₁-C₆)alkyl, halo(C₃-C₆)cycloalkyl, halo(C₄-C₇)cycloalkylalkyl, (C₁-C₆)alkoxy, (C₃-C₆)cycloalkoxy, (C₄-C₇)cycloalkylalkoxy, halo(C₁-C₆)alkoxy, halo(C₃-C₆)cycloalkoxy, halo(C₄-C₇)cycloalkylalkoxy, (C₁-C₆)alkylthio, (C₃-C₆)cycloalkylthio, (C₄-C₇)cycloalkylalkylthio, halo(C₁-C₆)alkylthio, halo(C₃-C₆)cycloalkylthio, halo(C₄-C₇)cycloalkylalkylthio, (C₁-C₆)alkanesulfinyl, (C₃-C₆)cycloalkanesulfinyl, (C₄-C₇)cycloalkylalkanesulfinyl, halo(C₁-C₆)alkanesulfinyl, halo(C₃-C₆)cycloalkanesulfinyl, halo(C₄-C₇)cycloalkylalkanesulfinyl, (C₁-C₆)alkanesulfonyl, (C₃-C₆)cycloalkanesulfonyl, (C₄-C₇)cycloalkylalkanesulfonyl, halo(C₁-C₆)alkanesulfonyl, halo(C₃-C₆)cycloalkanesulfonyl, halo(C₄-C₇)cycloalkylalkanesulfonyl, (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, (C₁-C₆)alkoxy(C₁-C₆)alkoxy, halo(C₁-C₆)alkoxy(C₁-C₆)alkoxy, (C₁-C₆)alkoxycarbonyl, H₂NCO, H₂NSO₂, (C₁-C₆)alkylaminocarbonyl, di(C₁-C₆)alkylaminocarbonyl, (C₁-C₃)alkoxy(C₁-C₃)alkylaminocarbonyl, heterocyclylcarbonyl, (C₁-C₆)alkylaminosulfonyl, di(C₁-C₆)alkylaminosulfonyl, heterocyclosulfonyl, (C₁-C₆)alkylcarbonylamino, (C₁-C₆)alkylcarbonylamino(C₁-C₆)alkyl, (C₁-C₆)alkylsulfonylamino, (C₁-C₆)alkylsulfonylamino(C₁-C₆)alkyl, (C₁-C₆)alkoxycarbonyl(C₁-C₆)alkoxy, (C₁-C₆)alkoxy(C₁-C₆)alkyl, halo(C₁-C₆)alkoxy(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkoxy, heteroaryl, oxo, amino(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)alkyl, di(C₁-C₆)alkylamino(C₁-C₆)alkyl amino(C₂-C₆)alkoxy, (C₁-C₆)alkylamino(C₂-C₆)alkoxy, di(C₁-C₆)alkylamino(C₂-C₆)alkoxy, (C₁-C₆)alkylcarbonyl, (C₃-C₆)cycloalkylcarbonyl, (C₃-C₆)cycloalkylaminocarbonyl, {(C₃-C₆)cycloalkyl}{(C₁-C₆)alkyl}aminocarbonyl, di(C₃-C₆)cycloalkylaminocarbonyl, (C₃-C₆)cycloalkylaminosulfonyl, {(C₃-C₆)cycloalkyl}{(C₁-C₆)alkyl}aminosulfonyl, di(C₃-C₆)cycloalkylaminosulfonyl, cyano(C₁-C₆)alkyl, aminocarbonyl(C₁-C₆)alkyl, (C₁-C₆)alkylaminocarbonyl(C₁-C₆)alkyl, di(C₁-C₆)alkylaminocarbonyl(C₁-C₆)alkyl, (C₃-C₆)cycloalkylaminocarbonyl(C₁-C₆)alkyl, {(C₃-C₆)cycloalkyl}{(C₁-C₆)alkyl}aminocarbonyl(C₁-C₆)alkyl and di(C₃-C₆)cycloalkylaminocarbonyl(C₁-C₆)alkyl;
- 30 E is (a) a bond or (b) (C₁-C₃)alkylene or (C₁-C₂)alkylenyloxy, wherein the O is attached to R², each of which is optionally substituted with 1 to 4 groups independently selected from methyl, ethyl, trifluoromethyl or oxo;

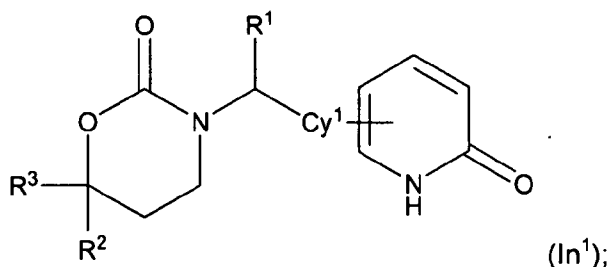
R^2 is (C₁-C₆)alkyl, aryl, heteroaryl, cycloalkyl or heterocyclyl and optionally substituted with up to 4 groups independently selected from fluorine, chlorine, bromine, iodine, cyano, nitro, amino, hydroxy, carboxy, (C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, hydroxy(C₃-C₆)cycloalkyl, (C₄-C₇)cycloalkylalkyl, (C₂-C₆)alkenyl, halo(C₂-C₆)alkenyl, hydroxy(C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₆)cycloalkyl(C₂-C₄)alkynyl, halo(C₁-C₆)alkyl, halo(C₃-C₆)cycloalkyl, halo(C₄-C₇)cycloalkylalkyl, (C₁-C₆)alkoxy, (C₃-C₆)cycloalkoxy, (C₄-C₇)cycloalkylalkoxy, halo(C₁-C₆)alkoxy, halo(C₃-C₆)cycloalkoxy, halo(C₄-C₇)cycloalkylalkoxy, (C₁-C₆)alkylthio, (C₃-C₆)cycloalkylthio, (C₄-C₇)cycloalkylalkylthio, halo(C₁-C₆)alkylthio, halo(C₃-C₆)cycloalkylthio, halo(C₄-C₇)cycloalkylalkylthio, (C₁-C₆)alkanesulfinyl, (C₃-C₆)cycloalkanesulfinyl, (C₄-C₇)cycloalkylalkanesulfinyl, halo(C₁-C₆)alkanesulfinyl, halo(C₃-C₆)cycloalkanesulfinyl, halo(C₄-C₇)cycloalkylalkanesulfinyl, (C₁-C₆)alkanesulfonyl, (C₃-C₆)cycloalkanesulfonyl, (C₄-C₇)cycloalkylalkanesulfonyl, halo(C₁-C₆)alkanesulfonyl, halo(C₃-C₆)cycloalkanesulfonyl, halo(C₄-C₇)cycloalkylalkanesulfonyl, (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, (C₁-C₆)alkoxy(C₁-C₆)alkoxy, halo(C₁-C₆)alkoxy(C₁-C₆)alkoxy, (C₁-C₆)alkoxycarbonyl, H₂NCO, H₂NSO₂, (C₁-C₆)alkylaminocarbonyl, di(C₁-C₆)alkylaminocarbonyl, (C₁-C₃)alkoxy(C₁-C₃)alkylaminocarbonyl, heterocyclylcarbonyl, (C₁-C₆)alkylaminosulfonyl, di(C₁-C₆)alkylaminosulfonyl, heterocyclosulfonyl, (C₁-C₆)alkylcarbonylamino, (C₁-C₆)alkylcarbonylamino(C₁-C₆)alkyl, (C₁-C₆)alkylsulfonylamino, (C₁-C₆)alkylsulfonylamino(C₁-C₆)alkyl, (C₁-C₆)alkoxycarbonyl(C₁-C₆)alkoxy, (C₁-C₆)alkoxy(C₁-C₆)alkyl, halo(C₁-C₆)alkoxy(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkoxy, heteroaryl, oxo, amino(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)alkyl, di(C₁-C₆)alkylamino(C₁-C₆)alkyl amino(C₂-C₆)alkoxy, (C₁-C₆)alkylamino(C₂-C₆)alkoxy, di(C₁-C₆)alkylamino(C₂-C₆)alkoxy, (C₁-C₆)alkylcarbonyl, (C₃-C₆)cycloalkylcarbonyl, (C₃-C₆)cycloalkylaminocarbonyl, {(C₃-C₆)cycloalkyl}{(C₁-C₆)alkyl}aminocarbonyl, di(C₃-C₆)cycloalkylaminocarbonyl, (C₃-C₆)cycloalkylaminosulfonyl, {(C₃-C₆)cycloalkyl}{(C₁-C₆)alkyl}aminosulfonyl, di(C₃-C₆)cycloalkylaminosulfonyl, cyano(C₁-C₆)alkyl, aminocarbonyl(C₁-C₆)alkyl, (C₁-C₆)alkylaminocarbonyl(C₁-C₆)alkyl, di(C₁-C₆)alkylaminocarbonyl(C₁-C₆)alkyl, (C₃-C₆)cycloalkylaminocarbonyl(C₁-C₆)alkyl, {(C₃-C₆)cycloalkyl}{(C₁-C₆)alkyl}aminocarbonyl(C₁-C₆)alkyl and di(C₃-C₆)cycloalkylaminocarbonyl(C₁-C₆)alkyl;

R^3 is selected from (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₆)cycloalkyl(C₁-C₄)alkyl, (C₁-C₃)alkoxy(C₁-C₃)alkoxy, or (C₁-C₃)alkoxy(C₁-C₃)alkyl and is optionally substituted with up to four groups independently selected from fluorine, cyano, oxo, R^4 ,

- R^4O- , $(R^4)_2N-$, R^4O_2C- , $R^4C(=O)O-$, R^4S , $R^4S(=O)-$, $R^4S(=O)_2-$, $R^4C(=O)NR^4-$,
 $(R^4)_2NC(=O)-$, $(R^4)_2NC(=O)O-$, $(R^4)_2NC(=O)NR^4-$, $R^4OC(=O)NR^4-$, $(R^4)_2NC(=NCN)NR^4-$,
 $(R^4O)_2P(=O)O-$, $(R^4O)_2P(=O)NR^4-$, $R^4OS(=O)_2NR^4-$, $(R^4)_2NS(=O)_2O-$, $(R^4)_2NS(=O)_2NR^4-$,
 $R^4S(=O)_2NR^4-$, $R^4S(=O)_2NHC(=O)-$, $R^4S(=O)_2NHC(=O)O-$, $R^4S(=O)_2NHC(=O)NR^4-$,
5 $R^4OS(=O)_2NHC(=O)-$, $R^4OS(=O)_2NHC(=O)O-$, $R^4OS(=O)_2NHC(=O)NR^4-$,
 $(R^4)_2NS(=O)_2NHC(=O)-$, $(R^4)_2NS(=O)_2NHC(=O)O-$, $(R^4)_2NS(=O)_2NHC(=O)NR^4-$,
 $R^4C(=O)NHS(=O)_2-$, $R^4C(=O)NHS(=O)_2O-$, $R^4C(=O)NHS(=O)_2NR^4-$,
 $R^4OC(=O)NHS(=O)_2-$, $R^4OC(=O)NHS(=O)_2O-$, $R^4OC(=O)NHS(=O)_2NR^4-$,
 $(R^4)_2NC(=O)NHS(=O)_2-$, $(R^4)_2NC(=O)NHS(=O)_2O-$, $(R^4)_2NC(=O)NHS(=O)_2NR^4-$,
10 spirocycloalkyl; heterocyclyl (optionally substituted with alkyl, haloalkyl, halogen or oxo),
heteroaryl (optionally substituted with alkyl, haloalkyl, alkoxy, alkylthio, alkylsulfonyl,
halogen, trifluoromethyl, dialkylamino, nitro, cyano, CO_2H , $CONH_2$, N-monoalkyl-
substituted amido, N,N-dialkyl-substituted amido, or oxo), arylamino (optionally
substituted with alkyl, alkoxy, alkylthio, alkylsulfonyl, halogen, trifluoromethyl,
15 dialkylamino, nitro, cyano, CO_2H , $CONH_2$, N-monoalkyl-substituted amido and N,N-
dialkyl-substituted amido) and heteroarylamino (optionally substituted with alkyl,
haloalkyl, alkoxy, alkylthio, alkylsulfonyl, halogen, trifluoromethyl, dialkylamino, nitro,
cyano, CO_2H , $CONH_2$, N-monoalkyl-substituted amido, N,N-dialkyl-substituted amido, or
oxo); and
20 R^4 is independently selected from H, (C_1-C_6) alkyl, halo (C_1-C_6) alkyl, amino (C_1-C_6) alkyl,
 (C_1-C_6) alkylamino (C_1-C_6) alkyl, di (C_1-C_6) alkylamino (C_1-C_6) alkyl, hydroxy (C_1-C_6) alkyl and
 (C_1-C_6) alkoxy (C_1-C_6) alkyl;
or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof;
provided that the compound is not a compound represented by structural formulas PR-
25 221 or PR-313, or a pharmaceutically acceptable salt, enantiomer or diastereomer
thereof.

2. The compound of claim 1, wherein the compound is of Formula (In¹):

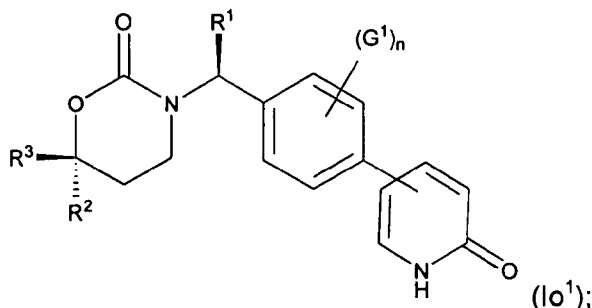
- 180 -



or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

3. The compound of claim 2, wherein the compound is of Formula (Io¹):

5



or a pharmaceutically acceptable salt thereof;

wherein:

n is 0, 1, 2 or 3; and

- 10 G¹ is fluorine, chlorine, bromine, iodine, cyano, nitro, amino, hydroxy, carboxy, (C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, hydroxy(C₃-C₆)cycloalkyl, (C₄-C₇)cycloalkylalkyl, (C₂-C₆)alkenyl, halo(C₂-C₆)alkenyl, hydroxy(C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₆)cycloalkyl(C₂-C₄)alkynyl, halo(C₁-C₆)alkyl, halo(C₃-C₆)cycloalkyl, halo(C₄-C₇)cycloalkylalkyl, (C₁-C₆)alkoxy, (C₃-C₆)cycloalkoxy, (C₄-C₇)cycloalkylalkoxy,
- 15 halo(C₁-C₆)alkoxy, halo(C₃-C₆)cycloalkoxy, halo(C₄-C₇)cycloalkylalkoxy, (C₁-C₆)alkylthio, (C₃-C₆)cycloalkylthio, (C₄-C₇)cycloalkylalkylthio, halo(C₁-C₆)alkylthio, halo(C₃-C₆)cycloalkylthio, halo(C₄-C₇)cycloalkylalkylthio, (C₁-C₆)alkanesulfinyl, (C₃-C₆)cycloalkanesulfinyl, (C₄-C₇)cycloalkylalkanesulfinyl, halo(C₁-C₆)alkanesulfinyl, halo(C₃-C₆)cycloalkanesulfinyl, halo(C₄-C₇)cycloalkylalkanesulfinyl, (C₁-
- 20 C₆)alkanesulfonyl, (C₃-C₆)cycloalkanesulfonyl, (C₄-C₇)cycloalkylalkanesulfonyl, halo(C₁-C₆)alkanesulfonyl, halo(C₃-C₆)cycloalkanesulfonyl, halo(C₄-C₇)cycloalkylalkanesulfonyl, (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, (C₁-C₆)alkoxy(C₁-C₆)alkoxy, halo(C₁-C₆)alkoxy(C₁-C₆)alkoxy, (C₁-C₆)alkoxycarbonyl, H₂NCO, H₂NSO₂,

(C₁-C₆)alkylaminocarbonyl, di(C₁-C₆)alkylaminocarbonyl, (C₁-C₃)alkoxy(C₁-C₃)alkylaminocarbonyl, heterocyclylcarbonyl, (C₁-C₆)alkylaminosulfonyl, di(C₁-C₆)alkylaminosulfonyl, heterocyclosulfonyl, (C₁-C₆)alkylcarbonylamino, (C₁-C₆)alkylcarbonylamino(C₁-C₆)alkyl, (C₁-C₆)alkylsulfonylamino, (C₁-C₆)alkylsulfonylamino(C₁-C₆)alkyl, (C₁-C₆)alkoxy-carbonyl(C₁-C₆)alkoxy, (C₁-C₆)alkoxy(C₁-C₆)alkyl, halo(C₁-C₆)alkoxy(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkoxy, heteroaryl, amino(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)alkyl, di(C₁-C₆)alkylamino(C₁-C₆)alkyl amino(C₂-C₆)alkoxy, (C₁-C₆)alkylamino(C₂-C₆)alkoxy, di(C₁-C₆)alkylamino(C₂-C₆)alkoxy, (C₁-C₆)alkylcarbonyl, (C₃-C₆)cycloalkylcarbonyl, (C₃-C₆)cycloalkylaminocarbonyl, {(C₃-C₆)cycloalkyl}{(C₁-C₆)alkyl}aminocarbonyl, di(C₃-C₆)cycloalkylaminocarbonyl, (C₃-C₆)cycloalkylaminosulfonyl, {(C₃-C₆)cycloalkyl}{(C₁-C₆)alkyl}aminosulfonyl, di(C₃-C₆)cycloalkylaminosulfonyl, cyano(C₁-C₆)alkyl, aminocarbonyl(C₁-C₆)alkyl, (C₁-C₆)alkylaminocarbonyl(C₁-C₆)alkyl, di(C₁-C₆)alkylaminocarbonyl(C₁-C₆)alkyl, (C₃-C₆)cycloalkylaminocarbonyl(C₁-C₆)alkyl, {(C₃-C₆)cycloalkyl}{(C₁-C₆)alkyl}aminocarbonyl(C₁-C₆)alkyl and di(C₃-C₆)cycloalkylaminocarbonyl(C₁-C₆)alkyl.

4. The compound of claim 3, wherein:

n is 0, 1, 2 or 3;

G¹ is (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkyl, (C₁-C₄)haloalkoxy, halogen, cyano or nitro;

the oxodihydropyridyl in Formula 1o² is optionally substituted on a substitutable ring nitrogen atom with C₁-C₄ alkyl, (C₃-C₄)cycloalkyl, (C₃-C₄)cycloalkyl(C₁-C₂)alkyl or C₁-C₄ haloalkyl; and

the oxodihydropyridyl in Formula 1o² is optionally substituted on a ring carbon atom with fluorine, chlorine, cyano, hydroxy, amino, (C₁-C₄)alkyl, (C₃-C₄)cycloalkyl, (C₃-C₄)cycloalkyl(C₁-C₂)alkyl, halo(C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkoxy, CONH₂, (C₁-C₄)alkylaminocarbonyl, di(C₁-C₄)alkylaminocarbonyl or (C₁-C₄)alkylcarbonylamino.

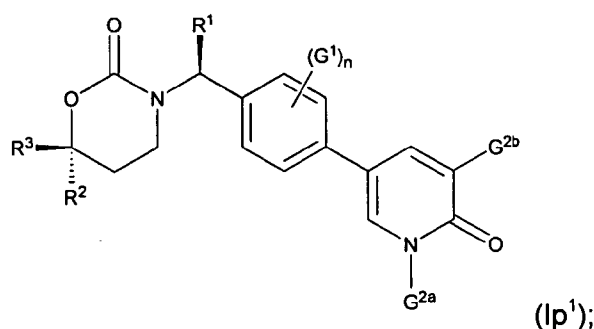
5. The compound of claim 4, wherein R¹ is methyl or ethyl.

6. The compound of claim 4, wherein R¹ is methyl or ethyl; and R³ is MeSO₂NHCH₂CH₂CH₂, H₂NC(=O)CH₂CH₂, H₂NC(=O)CMe₂CH₂, 3-hydroxypropyl, 3-

hydroxy-3-methylbutyl, 2-hydroxyethyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

7. The compound of claim 4, wherein R^1 is methyl or ethyl; R^2 is phenyl optionally substituted with 1, 2 or 3 substituents selected from halo, cyano, CONH_2 , $(\text{C}_1\text{-C}_4)\text{alkyl}$, $(\text{C}_1\text{-C}_4)\text{haloalkyl}$ and SO_2Me ; and R^3 is $\text{MeSO}_2\text{NHCH}_2\text{CH}_2\text{CH}_2$, $\text{H}_2\text{NC(=O)CH}_2\text{CH}_2$, $\text{H}_2\text{NC(=O)CMe}_2\text{CH}_2$, 3-hydroxypropyl, 3-hydroxy-3-methylbutyl, 2-hydroxyethyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

8. The compound of claim 3, wherein the compound is of Formula (Ip^1):



or a pharmaceutically acceptable salt thereof; and
wherein:

G^1 is $(\text{C}_1\text{-C}_4)\text{alkyl}$, $(\text{C}_1\text{-C}_4)\text{alkoxy}$, $(\text{C}_1\text{-C}_4)\text{haloalkyl}$, $(\text{C}_1\text{-C}_4)\text{haloalkoxy}$, halogen, cyano or nitro;

n is 0, 1 or 2;

G^{2a} is $(\text{C}_1\text{-C}_4)\text{alkyl}$, $(\text{C}_3\text{-C}_4)\text{cycloalkyl}$ or $(\text{C}_1\text{-C}_4)\text{haloalkyl}$;

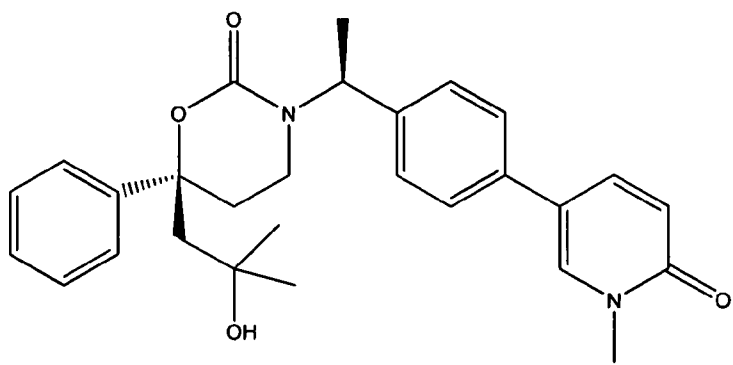
G^{2b} is hydrogen, fluorine, chlorine, cyano, hydroxy, amino, $(\text{C}_1\text{-C}_4)\text{alkyl}$, $(\text{C}_3\text{-C}_4)\text{cycloalkyl}$, $(\text{C}_3\text{-C}_4)\text{cycloalkyl}(\text{C}_1\text{-C}_2)\text{alkyl}$, halo $(\text{C}_1\text{-C}_4)\text{alkyl}$, $(\text{C}_1\text{-C}_4)\text{alkoxy}$, $(\text{C}_1\text{-C}_4)\text{haloalkoxy}$, CONH_2 , $(\text{C}_1\text{-C}_4)\text{alkylaminocarbonyl}$, di $(\text{C}_1\text{-C}_4)\text{alkylaminocarbonyl}$ or $(\text{C}_1\text{-C}_4)\text{alkylcarbonylamino}$.

9. The compound of claim 8, wherein R^1 is methyl or ethyl.

10. The compound of claim 8, wherein R^1 is methyl or ethyl; and R^3 is $\text{MeSO}_2\text{NHCH}_2\text{CH}_2\text{CH}_2$, $\text{H}_2\text{NC(=O)CH}_2\text{CH}_2$, $\text{H}_2\text{NC(=O)CMe}_2\text{CH}_2$, 3-hydroxypropyl, 3-

hydroxy-3-methylbutyl, 2-hydroxyethyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

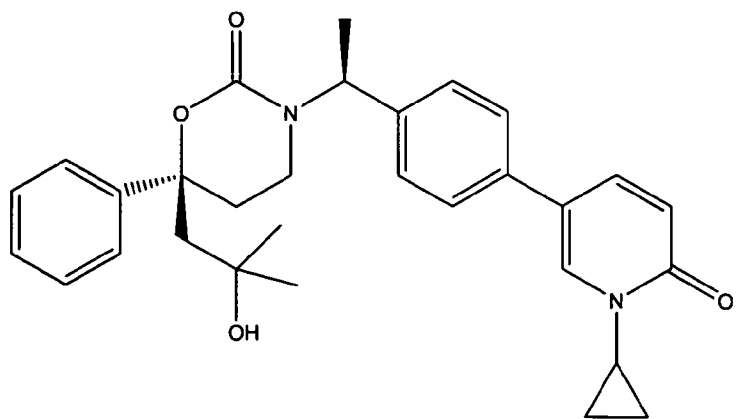
11. The compound of claim 8, wherein R^1 is methyl or ethyl; R^2 is phenyl optionally substituted with 1, 2 or 3 substituents selected from halo, cyano, CONH_2 , $(\text{C}_1\text{-C}_4)\text{alkyl}$, $(\text{C}_1\text{-C}_4)\text{haloalkyl}$ and SO_2Me ; and R^3 is $\text{MeSO}_2\text{NHCH}_2\text{CH}_2\text{CH}_2$, $\text{H}_2\text{NC(=O)CH}_2\text{CH}_2$, $\text{H}_2\text{NC(=O)CMe}_2\text{CH}_2$, 3-hydroxypropyl, 3-hydroxy-3-methylbutyl, 2-hydroxyethyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.
12. The compound of claim 8, wherein R^1 is methyl or ethyl; R^2 is phenyl or fluorophenyl; R^3 is 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl; the substituent G^{2a} is selected from $(\text{C}_1\text{-C}_4)\text{alkyl}$, $(\text{C}_3\text{-C}_4)\text{cycloalkyl}$, $(\text{C}_3\text{-C}_4)\text{cycloalkyl}(\text{C}_1\text{-C}_2)\text{alkyl}$, and $(\text{C}_1\text{-C}_2)\text{haloalkyl}$; and G^{2b} is optionally selected from hydrogen, methyl or ethyl.
13. The compound of claim 12, wherein the compound is of the following Formula:



or a pharmaceutically acceptable salt thereof.

14. The compound of claim 12, wherein the compound is of the following Formula:

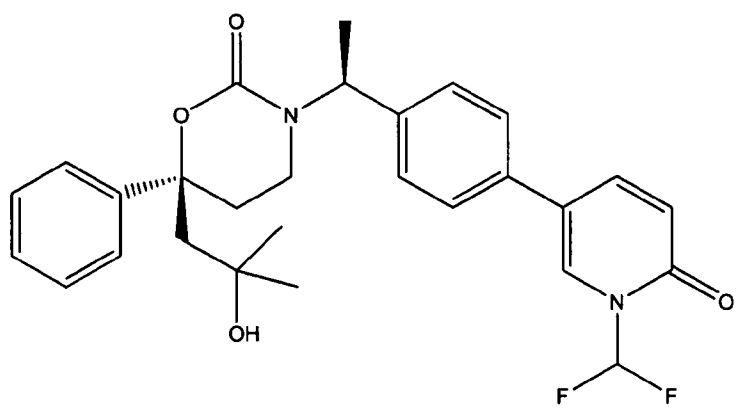
- 184 -



or a pharmaceutically acceptable salt thereof.

15. The compound of claim 12, wherein the compound is of the following Formula:

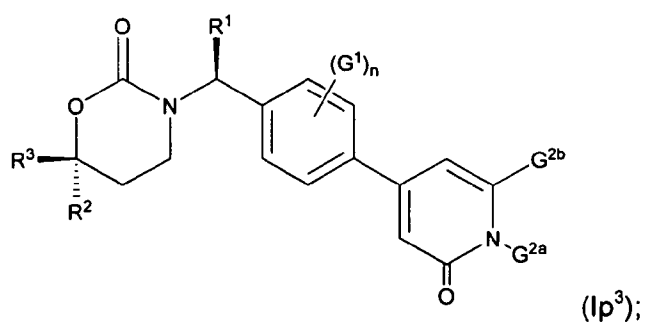
5



or a pharmaceutically acceptable salt thereof.

16. The compound of claim 3, wherein the compound is of Formula (Ip³):

10



or a pharmaceutically acceptable salt; and

wherein:

G¹ is (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkyl, (C₁-C₄)haloalkoxy, halogen, cyano or nitro;

n is 0, 1 or 2;

5 G^{2a} is (C₁-C₄)alkyl, (C₃-C₄)cycloalkyl or (C₁-C₄)haloalkyl;

G^{2b} is hydrogen, fluorine, chlorine, cyano, hydroxy, amino, (C₁-C₄)alkyl, (C₃-C₄)cycloalkyl, (C₃-C₄)cycloalkyl(C₁-C₂)alkyl, halo(C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkoxy, CONH₂, (C₁-C₄)alkylaminocarbonyl, di(C₁-C₄)alkylaminocarbonyl or (C₁-C₄)alkylcarbonylamino.

10

17. The compound of claim 16, wherein R¹ is methyl or ethyl.

18. The compound of claim 16, wherein R¹ is methyl or ethyl; and R³ is MeSO₂NHCH₂CH₂CH₂, H₂NC(=O)CH₂CH₂, H₂NC(=O)CMe₂CH₂, 3-hydroxypropyl, 3-hydroxy-3-methylbutyl, 2-hydroxyethyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

15

19. The compound of claim 16, wherein R¹ is methyl or ethyl; R² is phenyl optionally substituted with 1, 2 or 3 substituents selected from halo, cyano, CONH₂, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl and SO₂Me; and R³ is MeSO₂NHCH₂CH₂CH₂, H₂NC(=O)CH₂CH₂, H₂NC(=O)CMe₂CH₂, 3-hydroxypropyl, 3-hydroxy-3-methylbutyl, 2-hydroxyethyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

20

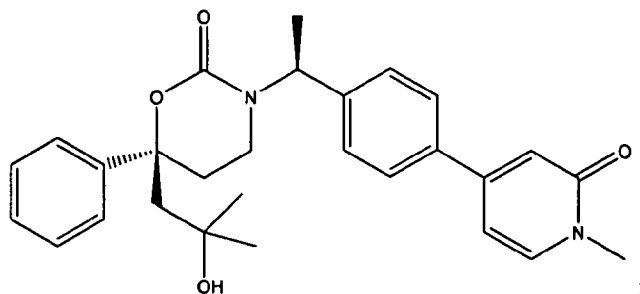
20. The compound of claim 16, wherein R¹ is methyl or ethyl; R² is phenyl or fluorophenyl; R³ is 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl; the substituent G^{2a} is selected from (C₁-C₄)alkyl, (C₃-C₄)cycloalkyl, (C₃-C₄)cycloalkyl(C₁-C₂)alkyl, and (C₁-C₂)haloalkyl; and G^{2b} is optionally selected from hydrogen, methyl or ethyl.

25

21. The compound of claim 20, wherein the compound is of the following Formula:

30

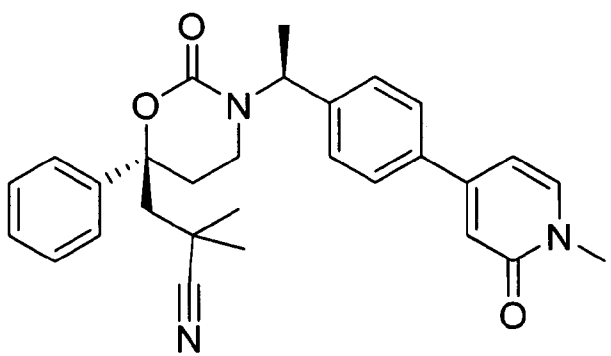
- 186 -



or a pharmaceutically acceptable salt.

22. The compound of claim 20, wherein the compound is of the following Formula:

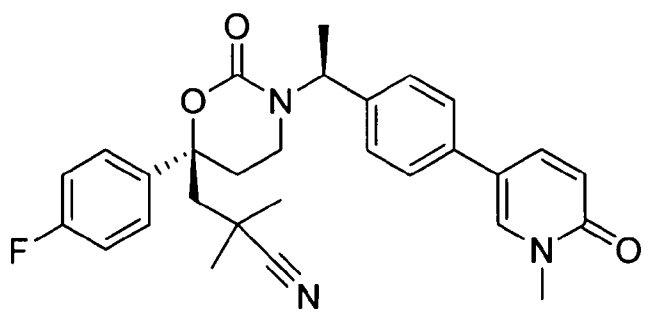
5



or a pharmaceutically acceptable salt.

23. The compound of claim 20, wherein the compound is of the following Formula:

10

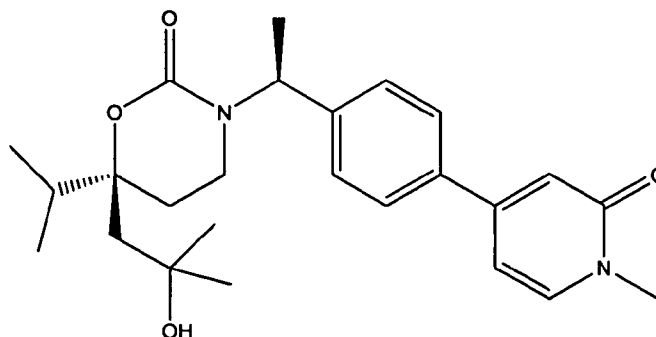


or a pharmaceutically acceptable salt.

24. The compound of claim 20, wherein the compound is of the following Formula:

15

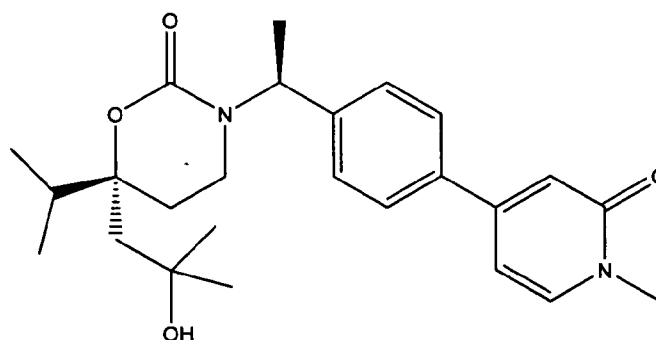
- 187 -



or a pharmaceutically acceptable salt.

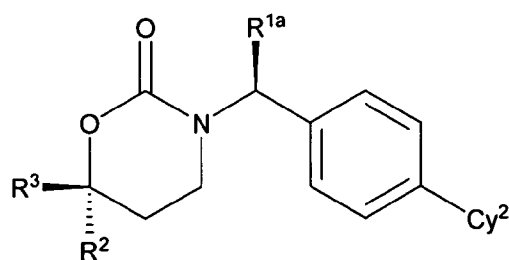
25. The compound of claim 20, wherein the compound is of the following Formula:

5



or a pharmaceutically acceptable salt.

26. The compound of claim 1, wherein the compound is of Formula (Ik):

**Ik**

;

10

R^{1a} is absent or is methyl or ethyl;

Cy^2 is 2-oxo-1,2-dihydropyridyl optionally substituted by 1 to 4 groups independently

15 selected from halo, hydroxy, methoxy, hydroxymethyl, methoxycarbonyl, amino,

carbamoyl, methylcarbamoyl, dimethylcarbamoyl, (2-methoxyethyl)aminocarbonyl, acetylaminomethyl, methylsulfonyl, methylsulfonylamino, methylaminosulfonyl, isopropylaminosulfonyl, dimethylaminosulfonyl, pyrrolidine-1-sulfonyl, methylsulfonylaminomethyl, tetrazolyl, methyl, trifluoromethyl, acetyl, 2-hydroxyethyl and
 5 1-aminoethyl;

R² is phenyl, thienyl, pyridyl or isopropyl each optionally substituted with halo, methyl, methylthio or (4-morpholino)methyl; and

R³ is methyl, ethyl, propyl, butyl, vinyl, allyl or ethoxyethyl each optionally substituted with up to two groups independently selected from Methyl, HO-, MeO-, H₂N-,

10 MeC(=O)NH-, MeS(=O)₂NH-, H₂NC(=O)-, MeNHC(=O)-, HO₂C-, (HO)₂P(=O)O-, H₂NS(=O)₂O-, H₂NS(=O)₂NH-, MeNHC(=O)NH-, MeNHC(=O)O-, oxo, cyano, HO₂C-, HOCH₂CH₂NH-, 4-morpholino, HOCH₂C(=O)NH-, H₂NCH₂C(=O)NH-, EtNHC(=O)NH, MeOC(=O)NH-, MeNHC(=NC≡N)NH-, Me-, MeS-, MeSO₂-, MeSO₂N(Me)-, MeS(=O)₂NHC(=O)-, imidazolylamino-, imidazolyl, tetrazolyl, H₂NCONH-, H₂NCO₂-,
 15 HOCH₂CH₂O-, MeNH-, Me₂N- and MeCONMe;

or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

27. A method of treating a subject with a disease associated with the activity or expression of 11β-HSD1, comprising the step of administering to the subject an effective
 20 amount of the compound in any one of claims 1-26.

28. A method of inhibiting 11β-HSD1 activity comprising the step of administering to a mammal in need of such treatment an effective amount of the compound in any one of
 25 claims 1-26.

29. A pharmaceutical composition comprising: i) a pharmaceutically acceptable carrier or diluent; and ii) the compound in any one of claims 1-26; or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

- 1 -

Date: <u>February 4, 2009</u> Express Mail Label No. <u>EV 214 932 719 US</u>

5

Inventors: David A. Claremon
Attorney's Docket No.: 4108.1013-001

CYCLIC INHIBITORS OF 11 β -HYDROXYSTEROID DEHYDROGENASE 1

10

FIELD OF THE INVENTION

The present invention relates to inhibitors of 11 β -hydroxysteroid dehydrogenase type 1 (11 β -HSD1), pharmaceutical compositions thereof and methods of using the same.

15

BACKGROUND OF THE INVENTION

Glucocorticoids, such as cortisol (hydrocortisone), are steroid hormones that regulate fat metabolism, function and distribution, and play a role in carbohydrate, protein and fat metabolism. Glucocorticoids are also known to have physiological effects on development, neurobiology, inflammation, blood pressure, metabolism, and programmed cell death. Cortisol and other corticosteroids bind both the glucocorticoid receptor (GR) and the mineralocorticoid receptor (MR), which are members of the nuclear hormone receptor superfamily and have been shown to mediate cortisol function in vivo. These receptors directly modulate transcription via DNA-binding zinc finger domains and transcriptional activation domains.

25

Until recently, the major determinants of glucocorticoid action were attributed to three primary factors: (1) circulating levels of glucocorticoid (driven primarily by the hypothalamic-pituitary-adrenal (HPA) axis); (2) protein binding of glucocorticoids in circulation; and (3) intracellular receptor density inside target tissues. Recently, a fourth determinant of glucocorticoid function has been identified: tissue-specific pre-receptor metabolism by glucocorticoid-activating and -inactivating enzymes. These 11 β -hydroxysteroid dehydrogenase (11 β -HSD) pre-receptor control enzymes modulate

30

activation of GR and MR by regulation of glucocorticoid hormones. To date, two distinct isozymes of 11-beta-HSD have been cloned and characterized: 11 β -HSD1 (also known as 11-beta-HSD type 1, 11betaHSD1, HSD11B1, HDL, and HSD11L) and 11 β -HSD2.

11 β -HSD1 is a bi-directional oxidoreductase that regenerates active cortisol from

- 5 inactive 11-keto forms, whereas 11 β -HSD2 is a unidirectional dehydrogenase that inactivates biologically active cortisol by converting it into cortisone.

The two isoforms are expressed in a distinct tissue-specific fashion, consistent with the differences in their physiological roles. 11 β -HSD1 is widely distributed in rat and human tissues; expression of the enzyme and corresponding mRNA have been detected

- 10 in human liver, adipose tissue, lung, testis, bone and ciliary epithelium. In adipose tissue, increased cortisol concentrations stimulate adipocyte differentiation and may play a role in promoting visceral obesity. In the eye, 11 β -HSD1 may regulate intraocular pressure and may contribute to glaucoma; some data suggest that inhibition of 11 β -HSD1 may cause a drop in intraocular pressure in patients with intraocular hypertension
- 15 (Kotelevstev et al. (1997), Proc. Natl. Acad. Sci. USA 94(26):14924-9). Although 11 β -HSD1 catalyzes both 11-beta-dehydrogenation and the reverse 11-oxoreduction reaction, 11 β -HSD1 acts predominantly as a NADPH-dependent oxoreductase in intact cells and tissues, catalyzing the formation of active cortisol from inert cortisone (Low et al. (1994) J. Mol. Endocrin. 13: 167-174). In contradistinction, 11 β -HSD2 expression is
- 20 found mainly in mineralocorticoid target tissues such as kidney (cortex and medulla), placenta, sigmoid and rectal colon, salivary gland and colonic epithelial cell lines. 11 β -HSD2 acts as an NAD-dependent dehydrogenase catalyzing the inactivation of cortisol to cortisone (Albiston et al. (1994) Mol. Cell. Endocrin. 105: R11-R17), and has been shown to protect the MR from glucocorticoid excess (e.g., high levels of receptor-active
- 25 cortisol) (Blum, et al. (2003) Prog. Nucl. Acid Res. Mol. Biol. 75:173-216).

Mutations in either the 11 β -HSD1 or the 11 β -HSD2 genes result in human pathology. For example, individuals with mutations in 11 β -HSD2 are deficient in this cortisol-inactivation activity and, as a result, present with a syndrome of apparent mineralocorticoid excess (also referred to as 'SAME') characterized by hypertension,

30 hypokalemia, and sodium retention (Edwards et al. (1988) Lancet 2: 986-989; Wilson et al. (1998) Proc. Natl. Acad. Sci. 95: 10200-10205). Similarly, mutations in 11 β -HSD1 and in the gene encoding a co-localized NADPH-generating enzyme, hexose 6-

phosphate dehydrogenase (H6PD), can result in cortisone reductase deficiency (CRD); these individuals present with ACTH-mediated androgen excess (hirsutism, menstrual irregularity, hyperandrogenism), a phenotype resembling polycystic ovary syndrome (PCOS) (Draper et al. (2003) *Nat. Genet.* 34: 434-439).

5 Notably, disruption of homeostasis in the HPA axis by either deficient or excess secretion or action results in Cushing's syndrome or Addison's disease, respectively (Miller and Chrousos (2001) *Endocrinology and Metabolism*, eds. Felig and Frohman (McGraw-Hill, New York), 4th Ed.: 387-524). Patients with Cushing's syndrome or receiving glucocorticoid therapy develop reversible visceral fat obesity. The phenotype
10 of Cushing's syndrome patients closely resembles that of Reaven's metabolic syndrome (also known as Syndrome X or insulin resistance syndrome), the symptoms of which include visceral obesity, glucose intolerance, insulin resistance, hypertension, type 2 diabetes and hyperlipidemia (Reaven (1993) *Ann. Rev. Med.* 44: 121-131). Although the role of glucocorticoids in human obesity is not fully characterized, there is mounting
15 evidence that 11 β -HSD1 activity plays an important role in obesity and metabolic syndrome (Bujalska et al. (1997) *Lancet* 349: 1210-1213); (Livingstone et al. (2000) *Endocrinology* 131: 560-563; Rask et al. (2001) *J. Clin. Endocrinol. Metab.* 86: 1418-1421; Lindsay et al. (2003) *J. Clin. Endocrinol. Metab.* 88: 2738-2744; Wake et al. (2003) *J. Clin. Endocrinol. Metab.* 88: 3983-3988).

20 Data from studies in mouse transgenic models supports the hypothesis that adipocyte 11 β -HSD1 activity plays a central role in visceral obesity and metabolic syndrome (Alberts et al. (2002) *Diabetologia*. 45(11): 1526-32). Over-expression in adipose tissue of 11 β -HSD1 under the control of the aP2 promoter in transgenic mice produced a phenotype remarkably similar to human metabolic syndrome (Masuzaki et
25 al. (2001) *Science* 294: 2166-2170; Masuzaki et al. (2003) *J. Clinical Invest.* 112: 83-90). Moreover, the increased activity of 11 β -HSD1 in these mice is very similar to that observed in human obesity (Rask et al. (2001) *J. Clin. Endocrinol. Metab.* 86: 1418-1421). In addition, data from studies with 11 β -HSD1-deficient mice produced by homologous recombination demonstrate that the loss of 11 β -HSD1 leads to an increase
30 in insulin sensitivity and glucose tolerance due to a tissue-specific deficiency in active glucocorticoid levels (Kotelevstev et al. (1997) *Proc. Natl. Acad. Sci.* 94: 14924-14929; Morton et al. (2001) *J. Biol. Chem.* 276: 41293-41300; Morton et al. (2004) *Diabetes* 53: 931-938).

The published data supports the hypothesis that increased expression of 11 β -HSD1 contributes to increased local conversion of cortisone to cortisol in adipose tissue and hence that 11 β -HSD1 plays a role in the pathogenesis of central obesity and the appearance of the metabolic syndrome in humans (Engeli, et al., (2004) *Obes. Res.* 12: 9-17). Therefore, 11 β -HSD1 is a promising pharmaceutical target for the treatment of the metabolic syndrome (Masuzaki, et al., (2003) *Curr. Drug Targets Immune Endocr. Metabol. Disord.* 3: 255-62). Furthermore, inhibition of 11 β -HSD1 activity may prove beneficial in treating numerous glucocorticoid-related disorders. For example, 11 β -HSD1 inhibitors could be effective in combating obesity and/or aspects of the metabolic syndrome cluster, including glucose intolerance, insulin resistance, hyperglycemia, hypertension, and/or hyperlipidemia (Kotelevstev et al. (1997) *Proc. Natl. Acad. Sci.* 94: 14924-14929; Morton et al. (2001) *J. Biol. Chem.* 276: 41293-41300; Morton et al. (2004) *Diabetes* 53: 931-938). In addition, inhibition of 11 β -HSD1 activity may have beneficial effects on the pancreas, including the enhancement of glucose-stimulated insulin release (Billaudel and Sutter (1979) *Horm. Metab. Res.* 11: 555-560; Ogawa et al. (1992) *J. Clin. Invest.* 90: 497-504; Davani et al. (2000) *J. Biol. Chem.* 275: 34841-34844).

Furthermore, given that inter-individual differences in general cognitive function have been linked to variability in the long-term exposure to glucocorticoids (Lupien et al. (1998) *Nat. Neurosci.* 1: 69-73) and dysregulation of the HPA axis resulting in chronic exposure to glucocorticoid excess in certain brain subregions has been theorized to contribute to the decline of cognitive function (McEwen and Sapolsky (1995) *Curr. Opin. Neurobiol.* 5: 205-216), one might predict that inhibition of 11 β -HSD1 could reduce exposure to glucocorticoids in the brain and thereby protect against deleterious glucocorticoid effects on neuronal function, including cognitive impairment, dementia, and/or depression. Notably, it is known that stress and glucocorticoids influence cognitive function (de Quervain et al. (1998) *Nature* 394: 787-790); and it has been shown that 11 β -HSD1, through its control of glucocorticoid action in the brain, may have effects on neurotoxicity (Rajan et al. (1996) *Neuroscience* 16: 65-70; Seckl (2000) *Neuroendocrinol.* 18:49-99).

There is also evidence that glucocorticoids and 11 β -HSD1 play a role in regulation of intra-ocular pressure (IOP) (Stokes et al. (2000) *Invest. Ophthalmol. Vis. Sci.* 41: 1629-1683; Rauz et al. (2001) *Invest. Ophthalmol. Vis. Sci.* 42: 2037-2042); if

left untreated, elevated IOP can lead to partial visual field loss and eventually blindness. Thus, inhibition of 11 β -HSD1 in the eye could reduce local glucocorticoid concentrations and IOP, and 11 β -HSD1 hence could potentially be used to treat glaucoma and other visual disorders.

5 Transgenic aP2-11 β HSD1 mice exhibit high arterial blood pressure and have increased sensitivity to dietary salt. Moreover, plasma angiotensinogen levels are elevated in the transgenic mice, as are angiotensin II and aldosterone; and treatment of the mice with an angiotensin II antagonist alleviates the hypertension (Masuzaki et al. (2003) J. Clinical Invest. 112: 83-90). This suggests that hypertension may be caused or
10 exacerbated by 11 β -HSD1 activity. Thus, 11 β -HSD1 inhibitors may be useful for treatment of hypertension and hypertension-related cardiovascular disorders. Inhibition of 11 β -HSD1 in mature adipocytes is also expected to attenuate secretion of plasminogen activator inhibitor 1 (PAI-1), which is an independent cardiovascular risk factor (Halleux et al. (1999) J. Clin. Endocrinol. Metabl. 84: 4097-4105).

15 Glucocorticoids can have adverse effects on skeletal tissues; and prolonged exposure to even moderate glucocorticoid doses can result in osteoporosis (Cannalis (1996) J. Clin. Endocrinol. Metab. 81: 3441-3447). In addition, 11 β -HSD1 has been shown to be present in cultures of human primary osteoblasts as well as cells from adult bone (Cooper et al. (2000) Bone 27: 375-381), and the 11 β -HSD1 inhibitor
20 carbenoxolone has been shown to attenuate the negative effects of glucocorticoids on bone nodule formation (Bellows et al. (1998) Bone 23: 119-125). Thus, inhibition of 11 β -HSD1 is predicted to decrease the local glucocorticoid concentration within osteoblasts and osteoclasts, thereby producing beneficial effects in various forms of bone disease, including osteoporosis.

25 11 β -HSD1 inhibitors may also be useful for immunomodulation. Although glucocorticoids are perceived to suppress the immune system, in actuality, there is a complex, dynamic interaction between the HPA axis and the immune system (Rook (1999) Baillier's Clin. Endocrinol. Metabl. 13: 576-581). Glucocorticoids play a role in modulating the balance between cell-mediated and humoral immune response, with high
30 glucocorticoid activity normally associated with a humoral response. Inhibition of 11 β -HSD1 therefore can be used a means of shifting the immune response towards a cell-mediated response. Certain disease states, such as tuberculosis, leprosy (Hansen's disease) and psoriasis, trigger immune responses that are biased towards a humoral

response whereas the more effective immune response may be a cell-mediated response. Hence, 11 β -HSD1 inhibitors may be useful for treating such diseases.

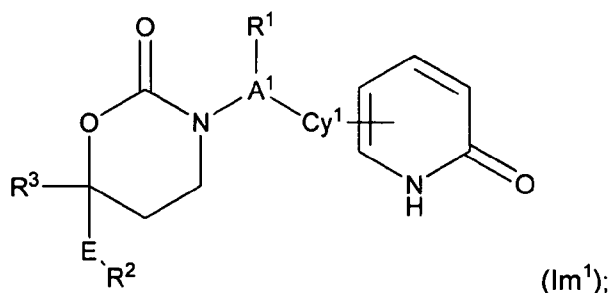
It has been reported that glucocorticoids inhibit wound healing, especially in diabetic patients with ulcers (Bitar et al. (1999) J. Surg. Res. 82: 234-243; Bitar et al. (1999) Surgery 125: 594-601; Bitar (2000) Surgery 127: 687-695; Bitar (1998) Am. J. Pathol. 152: 547-554). Patients that exhibit impaired glucose tolerance and/or type 2 diabetes often also have impaired wound healing. Glucocorticoids have been shown to increase the risk of infection and delay wound healing (Anstead (1998) Adv. Wound Care 11:277-285). Moreover, there is a correlation between elevated levels of cortisol in wound fluid and non-healing wounds (EP Patent App. No. 0 902 288). Recent published patent applications have suggested that certain 11 β -HSD1 inhibitors may be useful for promoting wound healing (PCT/US2006/043,951).

As evidenced herein, there is a continuing need for new and improved drugs that inhibit 11 β -HSD1. The novel compounds of the instant invention are effective inhibitors of 11 β -HSD1.

SUMMARY OF THE INVENTION

It has now been found that compounds of Formula Im¹ or pharmaceutically acceptable salts thereof, are effective inhibitors of 11 β -HSD1.

The invention is a compound represented by Formula (Im¹)



or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

In a first embodiment of the invention, Formula Im¹ and its constituent members are defined herein as follows:

R¹ is (a) absent or (b) is selected from (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₁-C₃)alkoxy(C₁-C₃)alkoxy, or (C₁-C₃)alkoxy(C₁-C₃)alkyl and is optionally

substituted with up to four groups independently selected from fluorine, cyano, oxo, R^4 , R^4O^- , $(R^4)_2N^-$, $R^4O_2C^-$, R^4S , $R^4S(=O)^-$, $R^4S(=O)_2^-$, $R^4C(=O)NR^4^-$, $(R^4)_2NC(=O)^-$, $(R^4)_2NC(=O)O^-$, $(R^4)_2NC(=O)NR^4^-$, $R^4OC(=O)NR^4^-$, $(R^4)_2NC(=NCN)NR^4^-$, $(R^4O)_2P(=O)O^-$, $(R^4O)_2P(=O)NR^4^-$, $R^4OS(=O)_2NR^4^-$, $(R^4)_2NS(=O)_2O^-$, $(R^4)_2NS(=O)_2NR^4^-$, $R^4S(=O)_2NR^4^-$, $R^4S(=O)_2NHC(=O)^-$, $R^4S(=O)_2NHC(=O)O^-$, $R^4S(=O)_2NHC(=O)NR^4^-$, $R^4OS(=O)_2NHC(=O)^-$, $R^4OS(=O)_2NHC(=O)O^-$, $R^4OS(=O)_2NHC(=O)NR^4^-$, $(R^4)_2NS(=O)_2NHC(=O)^-$, $(R^4)_2NS(=O)_2NHC(=O)O^-$, $(R^4)_2NS(=O)_2NHC(=O)NR^4^-$, $R^4C(=O)NHS(=O)_2^-$, $R^4C(=O)NHS(=O)_2O^-$, $R^4C(=O)NHS(=O)_2NR^4^-$, $R^4OC(=O)NHS(=O)_2^-$, $R^4OC(=O)NHS(=O)_2O^-$, $R^4OC(=O)NHS(=O)_2NR^4^-$, $(R^4)_2NC(=O)NHS(=O)_2^-$, $(R^4)_2NC(=O)NHS(=O)_2O^-$, $(R^4)_2NC(=O)NHS(=O)_2NR^4^-$, heterocyclyl, heteroaryl, arylamino and heteroarylamino;

A^1 is (a) a bond, or (b) (C_1-C_3) alkylene, CH_2CH_2O , wherein the oxygen is attached to Cy^1 , or $CH_2C(=O)$, wherein the carbonyl carbon is attached to Cy^1 ;

Cy^1 is aryl, heteroaryl, monocyclic cycloalkyl or monocyclic heterocyclyl and is optionally substituted with 1 to 4 groups independently selected from fluorine, chlorine, bromine, iodine, cyano, nitro, amino, hydroxy, carboxy, (C_1-C_6) alkyl, hydroxy (C_1-C_6) alkyl, (C_3-C_6) cycloalkyl, hydroxy (C_3-C_6) cycloalkyl, (C_4-C_7) cycloalkylalkyl, (C_2-C_6) alkenyl, halo (C_2-C_6) alkenyl, hydroxy (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, (C_3-C_6) cycloalkyl (C_2-C_4) alkynyl, halo (C_1-C_6) alkyl, halo (C_3-C_6) cycloalkyl, halo (C_4-C_7) cycloalkylalkyl, (C_1-C_6) alkoxy, (C_3-C_6) cycloalkoxy, (C_4-C_7) cycloalkylalkoxy, halo (C_1-C_6) alkoxy, halo (C_3-C_6) cycloalkoxy, halo (C_4-C_7) cycloalkylalkoxy, (C_1-C_6) alkylthio, (C_3-C_6) cycloalkylthio, (C_4-C_7) cycloalkylalkylthio, halo (C_1-C_6) alkylthio, halo (C_3-C_6) cycloalkylthio, halo (C_4-C_7) cycloalkylalkylthio, (C_1-C_6) alkanesulfinyl, (C_3-C_6) cycloalkanesulfinyl, (C_4-C_7) cycloalkylalkanesulfinyl, halo (C_1-C_6) alkanesulfinyl, halo (C_3-C_6) cycloalkanesulfinyl, halo (C_4-C_7) cycloalkylalkanesulfinyl, (C_1-C_6) alkanesulfonyl, (C_3-C_6) cycloalkanesulfonyl, (C_4-C_7) cycloalkylalkanesulfonyl, halo (C_1-C_6) alkanesulfonyl, halo (C_3-C_6) cycloalkanesulfonyl, halo (C_4-C_7) cycloalkylalkanesulfonyl, (C_1-C_6) alkylamino, di (C_1-C_6) alkylamino, (C_1-C_6) alkoxy (C_1-C_6) alkoxy, halo (C_1-C_6) alkoxy (C_1-C_6) alkoxy, (C_1-C_6) alkoxycarbonyl, H_2NCO , H_2NSO_2 , (C_1-C_6) alkylaminocarbonyl, di (C_1-C_6) alkylaminocarbonyl, (C_1-C_3) alkoxy (C_1-C_3) alkylaminocarbonyl, heterocyclylcarbonyl, (C_1-C_6) alkylaminosulfonyl, di (C_1-C_6) alkylaminosulfonyl, heterocyclosulfonyl, (C_1-C_6) alkylcarbonylamino, (C_1-C_6) alkylcarbonylamino (C_1-C_6) alkyl, (C_1-C_6) alkylsulfonylamino, (C_1-C_6) alkylsulfonylamino $(C_1-$

- C₆)alkyl, (C₁-C₆)alkoxycarbonyl(C₁-C₆)alkoxy, (C₁-C₆)alkoxy(C₁-C₆)alkyl, halo(C₁-C₆)alkoxy(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkoxy, heteroaryl oxo, amino(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)alkyl, di(C₁-C₆)alkylamino(C₁-C₆)alkyl amino(C₂-C₆)alkoxy, (C₁-C₆)alkylamino(C₂-C₆)alkoxy, di(C₁-C₆)alkylamino(C₂-C₆)alkoxy, (C₁-C₆)alkylcarbonyl, (C₃-C₆)cycloalkylcarbonyl, (C₃-C₆)cycloalkylaminocarbonyl, {(C₃-C₆)cycloalkyl}{(C₁-C₆)alkyl}aminocarbonyl, di(C₃-C₆)cycloalkylaminocarbonyl, (C₃-C₆)cycloalkylaminosulfonyl, {(C₃-C₆)cycloalkyl}{(C₁-C₆)alkyl}aminosulfonyl, di(C₃-C₆)cycloalkylaminosulfonyl, cyano(C₁-C₆)alkyl, aminocarbonyl(C₁-C₆)alkyl, (C₁-C₆)alkylaminocarbonyl(C₁-C₆)alkyl, di(C₁-C₆)alkylaminocarbonyl(C₁-C₆)alkyl, (C₃-C₆)cycloalkylaminocarbonyl(C₁-C₆)alkyl, {(C₃-C₆)cycloalkyl}{(C₁-C₆)alkyl}aminocarbonyl(C₁-C₆)alkyl and di(C₃-C₆)cycloalkylaminocarbonyl(C₁-C₆)alkyl;

The oxodihydropyridyl ring in Formula Im¹ is optionally substituted with 1 to 4

groups independently selected from fluorine, chlorine, bromine, iodine, cyano, nitro, amino, hydroxy, carboxy, (C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, (C₃-C₆)cycloalkyl,

- hydroxy(C₃-C₆)cycloalkyl, (C₄-C₇)cycloalkylalkyl, (C₂-C₆)alkenyl, halo(C₂-C₆)alkenyl, hydroxy(C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₆)cycloalkyl(C₂-C₄)alkynyl, halo(C₁-C₆)alkyl, halo(C₃-C₆)cycloalkyl, halo(C₄-C₇)cycloalkylalkyl, (C₁-C₆)alkoxy, (C₃-C₆)cycloalkoxy, (C₄-C₇)cycloalkylalkoxy, halo(C₁-C₆)alkoxy, halo(C₃-C₆)cycloalkoxy, halo(C₄-C₇)cycloalkylalkoxy, (C₁-C₆)alkylthio, (C₃-C₆)cycloalkylthio, (C₄-C₇)cycloalkylalkylthio, halo(C₁-C₆)alkylthio, halo(C₃-C₆)cycloalkylthio, halo(C₄-C₇)cycloalkylalkylthio, (C₁-C₆)alkanesulfinyl, (C₃-C₆)cycloalkanesulfinyl, (C₄-C₇)cycloalkylalkanesulfinyl, halo(C₁-C₆)alkanesulfinyl, halo(C₃-C₆)cycloalkanesulfinyl, halo(C₄-C₇)cycloalkylalkanesulfinyl, (C₁-C₆)alkanesulfonyl, (C₃-C₆)cycloalkanesulfonyl, (C₄-C₇)cycloalkylalkanesulfonyl, halo(C₁-C₆)alkanesulfonyl, halo(C₃-C₆)cycloalkanesulfonyl, halo(C₄-C₇)cycloalkylalkanesulfonyl, (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, (C₁-C₆)alkoxy(C₁-C₆)alkoxy, halo(C₁-C₆)alkoxy(C₁-C₆)alkoxy, (C₁-C₆)alkoxycarbonyl, H₂NCO, H₂NSO₂, (C₁-C₆)alkylaminocarbonyl, di(C₁-C₆)alkylaminocarbonyl, (C₁-C₃)alkoxy(C₁-C₃)alkylaminocarbonyl, heterocyclylcarbonyl, (C₁-C₆)alkylaminosulfonyl, di(C₁-C₆)alkylaminosulfonyl, heterocyclosulfonyl, (C₁-C₆)alkylcarbonylamino, (C₁-C₆)alkylcarbonyl-amino(C₁-C₆)alkyl, (C₁-C₆)alkylsulfonylamino, (C₁-C₆)alkylsulfonylamino(C₁-C₆)alkyl, (C₁-C₆)alkoxycarbonyl(C₁-C₆)alkoxy, (C₁-C₆)alkoxy(C₁-C₆)alkyl, halo(C₁-C₆)alkoxy(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkoxy, heteroaryl, oxo, amino(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)alkyl, di(C₁-C₆)alkylamino(C₁-C₆)alkyl amino(C₂-C₆)alkoxy, (C₁-

C₆)alkylamino(C₂-C₆)alkoxy, di(C₁-C₆)alkylamino(C₂-C₆)alkoxy, (C₁-C₆)alkylcarbonyl, (C₃-C₆)cycloalkylcarbonyl, (C₃-C₆)cycloalkylaminocarbonyl, {(C₃-C₆)cycloalkyl}{(C₁-C₆)alkyl}aminocarbonyl, di(C₃-C₆)cycloalkylaminocarbonyl, (C₃-C₆)cycloalkylaminosulfonyl, {(C₃-C₆)cycloalkyl}{(C₁-C₆)alkyl}aminosulfonyl, di(C₃-C₆)cycloalkylaminosulfonyl, cyano(C₁-C₆)alkyl, aminocarbonyl(C₁-C₆)alkyl, (C₁-C₆)alkylaminocarbonyl(C₁-C₆)alkyl, di(C₁-C₆)alkylaminocarbonyl(C₁-C₆)alkyl, (C₃-C₆)cycloalkylaminocarbonyl(C₁-C₆)alkyl, {(C₃-C₆)cycloalkyl}{(C₁-C₆)alkyl}aminocarbonyl(C₁-C₆)alkyl and di(C₃-C₆)cycloalkylaminocarbonyl(C₁-C₆)alkyl;

E is (a) a bond or (b) (C₁-C₃)alkylene or (C₁-C₂)alkylenyloxy, wherein the O is attached to R², each of which is optionally substituted with 1 to 4 groups independently selected from methyl, ethyl, trifluoromethyl or oxo;

R² is (C₁-C₆)alkyl, aryl, heteroaryl, cycloalkyl or heterocyclyl and is optionally substituted with up to 4 groups independently selected from fluorine, chlorine, bromine, iodine, cyano, nitro, amino, hydroxy, carboxy, (C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, hydroxy(C₃-C₆)cycloalkyl, (C₄-C₇)cycloalkylalkyl, (C₂-C₆)alkenyl, halo(C₂-C₆)alkenyl, hydroxy(C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₆)cycloalkyl(C₂-C₄)alkynyl, halo(C₁-C₆)alkyl, halo(C₃-C₆)cycloalkyl, halo(C₄-C₇)cycloalkylalkyl, (C₁-C₆)alkoxy, (C₃-C₆)cycloalkoxy, (C₄-C₇)cycloalkylalkoxy, halo(C₁-C₆)alkoxy, halo(C₃-C₆)cycloalkoxy, halo(C₄-C₇)cycloalkylalkoxy, (C₁-C₆)alkylthio, (C₃-C₆)cycloalkylthio, (C₄-C₇)cycloalkylalkylthio, halo(C₁-C₆)alkylthio, halo(C₃-C₆)cycloalkylthio, halo(C₄-C₇)cycloalkylalkylthio, (C₁-C₆)alkanesulfinyl, (C₃-C₆)cycloalkanesulfinyl, (C₄-C₇)cycloalkylalkanesulfinyl, halo(C₁-C₆)alkanesulfinyl, halo(C₃-C₆)cycloalkanesulfinyl, halo(C₄-C₇)cycloalkylalkanesulfinyl, (C₁-C₆)alkanesulfonyl, (C₃-C₆)cycloalkanesulfonyl, (C₄-C₇)cycloalkylalkanesulfonyl, halo(C₁-C₆)alkanesulfonyl, halo(C₃-C₆)cycloalkanesulfonyl, halo(C₄-C₇)cycloalkylalkanesulfonyl, (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, (C₁-C₆)alkoxy(C₁-C₆)alkoxy, halo(C₁-C₆)alkoxy(C₁-C₆)alkoxy, (C₁-C₆)alkoxycarbonyl, H₂NCO, H₂NSO₂, (C₁-C₆)alkylaminocarbonyl, di(C₁-C₆)alkylaminocarbonyl, (C₁-C₃)alkoxy(C₁-C₃)alkylaminocarbonyl, heterocyclylcarbonyl, (C₁-C₆)alkylaminosulfonyl, di(C₁-C₆)alkylaminosulfonyl, heterocyclosulfonyl, (C₁-C₆)alkylcarbonylamino, (C₁-C₆)alkylcarbonylamino(C₁-C₆)alkyl, (C₁-C₆)alkylsulfonylamino, (C₁-C₆)alkylsulfonylamino(C₁-C₆)alkyl, (C₁-C₆)alkoxycarbonyl(C₁-C₆)alkoxy, (C₁-C₆)alkoxy(C₁-C₆)alkyl, halo(C₁-C₆)alkoxy(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkoxy, heteroaryl, oxo, amino(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)alkyl, di(C₁-C₆)alkylamino(C₁-C₆)alkyl amino(C₂-C₆)alkoxy, (C₁-

- C₆)alkylamino(C₂-C₆)alkoxy, di(C₁-C₆)alkylamino(C₂-C₆)alkoxy, (C₁-C₆)alkylcarbonyl, (C₃-C₆)cycloalkylcarbonyl, (C₃-C₆)cycloalkylaminocarbonyl, {(C₃-C₆)cycloalkyl}{(C₁-C₆)alkyl}aminocarbonyl, di(C₃-C₆)cycloalkylaminocarbonyl, (C₃-C₆)cycloalkylaminosulfonyl, {(C₃-C₆)cycloalkyl}{(C₁-C₆)alkyl}aminosulfonyl, di(C₃-C₆)cycloalkylaminosulfonyl, cyano(C₁-C₆)alkyl, aminocarbonyl(C₁-C₆)alkyl, (C₁-C₆)alkylaminocarbonyl(C₁-C₆)alkyl, di(C₁-C₆)alkylaminocarbonyl(C₁-C₆)alkyl, (C₃-C₆)cycloalkylaminocarbonyl(C₁-C₆)alkyl, {(C₃-C₆)cycloalkyl}{(C₁-C₆)alkyl}aminocarbonyl(C₁-C₆)alkyl and di(C₃-C₆)cycloalkylaminocarbonyl(C₁-C₆)alkyl;
- R³ is selected from (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₅)cycloalkyl(C₁-C₄)alkyl, (C₁-C₃)alkoxy(C₁-C₃)alkoxy, or (C₁-C₃)alkoxy(C₁-C₃)alkyl and is optionally substituted with up to four groups independently selected from fluorine, cyano, oxo, R⁴, R⁴O-, (R⁴)₂N-, R⁴O₂C-, R⁴C(=O)O-, R⁴S, R⁴S(=O)-, R⁴S(=O)₂-, R⁴C(=O)NR⁴-, (R⁴)₂NC(=O)-, (R⁴)₂NC(=O)O-, (R⁴)₂NC(=O)NR⁴-, R⁴OC(=O)NR⁴-, (R⁴)₂NC(=NCN)NR⁴-, (R⁴O)₂P(=O)O-, (R⁴O)₂P(=O)NR⁴-, R⁴OS(=O)₂NR⁴-, (R⁴)₂NS(=O)₂O-, (R⁴)₂NS(=O)₂NR⁴-, R⁴S(=O)₂NR⁴-, R⁴S(=O)₂NHC(=O)-, R⁴S(=O)₂NHC(=O)O-, R⁴S(=O)₂NHC(=O)NR⁴-, R⁴OS(=O)₂NHC(=O)-, R⁴OS(=O)₂NHC(=O)O-, R⁴OS(=O)₂NHC(=O)NR⁴-, (R⁴)₂NS(=O)₂NHC(=O)-, (R⁴)₂NS(=O)₂NHC(=O)O-, (R⁴)₂NS(=O)₂NHC(=O)NR⁴-, R⁴C(=O)NHS(=O)₂-, R⁴C(=O)NHS(=O)₂O-, R⁴C(=O)NHS(=O)₂NR⁴-, R⁴OC(=O)NHS(=O)₂-, R⁴OC(=O)NHS(=O)₂O-, R⁴OC(=O)NHS(=O)₂NR⁴-, (R⁴)₂NC(=O)NHS(=O)₂-, (R⁴)₂NC(=O)NHS(=O)₂O-, (R⁴)₂NC(=O)NHS(=O)₂NR⁴-, spirocycloalkyl; heterocyclyl (which in turn may be optionally substituted with alkyl, haloalkyl, halogen or oxo), heteroaryl (which in turn may be optionally substituted with alkyl, haloalkyl, alkoxy, alkylthio, alkylsulfonyl, halogen, trifluoromethyl, dialkylamino, nitro, cyano, CO₂H, CONH₂, N-monoalkyl-substituted amido, N,N-dialkyl-substituted amido, or oxo), arylamino (which in turn may be optionally substituted with alkyl, alkoxy, alkylthio, alkylsulfonyl, halogen, trifluoromethyl, dialkylamino, nitro, cyano, CO₂H, CONH₂, N-monoalkyl-substituted amido and N,N-dialkyl-substituted amido) and heteroarylamino (which in turn may be optionally substituted with alkyl, haloalkyl, alkoxy, alkylthio, alkylsulfonyl, halogen, trifluoromethyl, dialkylamino, nitro, cyano, CO₂H, CONH₂, N-monoalkyl-substituted amido, N,N-dialkyl-substituted amido, or oxo); and
- R⁴ is independently selected from H, (C₁-C₆)alkyl, halo(C₁-C₆)alkyl, amino(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)alkyl, di(C₁-C₆)alkylamino(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl and (C₁-C₆)alkoxy(C₁-C₆)alkyl.

Alternatively, the first embodiment above excludes the compounds of structural formulas PR-221 and PR-313, or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

Another embodiment of the invention is a pharmaceutical composition comprising
5 i) a pharmaceutically acceptable carrier or diluent, and ii) a compound of Formulas Ik, Im¹, Im², Im⁵, In¹, In², In⁵, Io¹, Io², Io⁵, Ip¹ or Ip³, or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

Another embodiment of the invention is a method of inhibiting 11 β -HSD1 activity comprising the step of administering to a mammal in need of such treatment an effective
10 amount of a compound of Formulas Ik, Im¹, Im², Im⁵, In¹, In², In⁵, Io¹, Io², Io⁵, Ip¹ or Ip³, or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

Another embodiment of the invention is a method of treating a subject with a disease associated with the activity or expression of 11 β -HSD1, comprising the step of administering to the subject an effective amount of a compound of Formulas Ik, Im¹, Im²,
15 Im⁵, In¹, In², In⁵, Io¹, Io², Io⁵, Ip¹ or Ip³, or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

Another embodiment of the invention is the use of a compound of Formulas Ik, Im¹, Im², Im⁵, In¹, In², In⁵, Io¹, Io², Io⁵, Ip¹ or Ip³, or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof for the manufacture of a medicament for inhibiting
20 11 β -HSD1 activity in a mammal in need of such treatment.

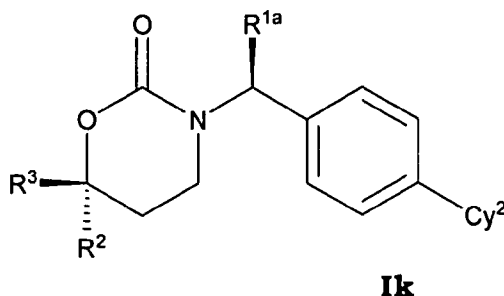
Another embodiment of the invention is the use of a compound of Formulas Ik, Im¹, Im², Im⁵, In¹, In², In⁵, Io¹, Io², Io⁵, Ip¹ or Ip³, or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof for the manufacture of a medicament for treating a subject with a disease associated with the activity or expression of 11 β -HSD1.

Another embodiment of the invention is a compound of Formulas Ik, Im¹, Im², Im⁵, In¹, In², In⁵, Io¹, Io², Io⁵, Ip¹ or Ip³, or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof for use in inhibiting 11 β -HSD1 activity in a mammal in need of such treatment.

Another embodiment of the invention is a compound of Ik, Im¹, Im², Im⁵, In¹, In², In⁵, Io¹, Io², Io⁵, Ip¹ or Ip³, or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof for use in for treating a subject with a disease associated with the activity or expression of 11 β -HSD1.
30

DETAILED DESCRIPTION OF THE INVENTION

Another embodiment of the invention is a compound of Formula Ik:



or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof;

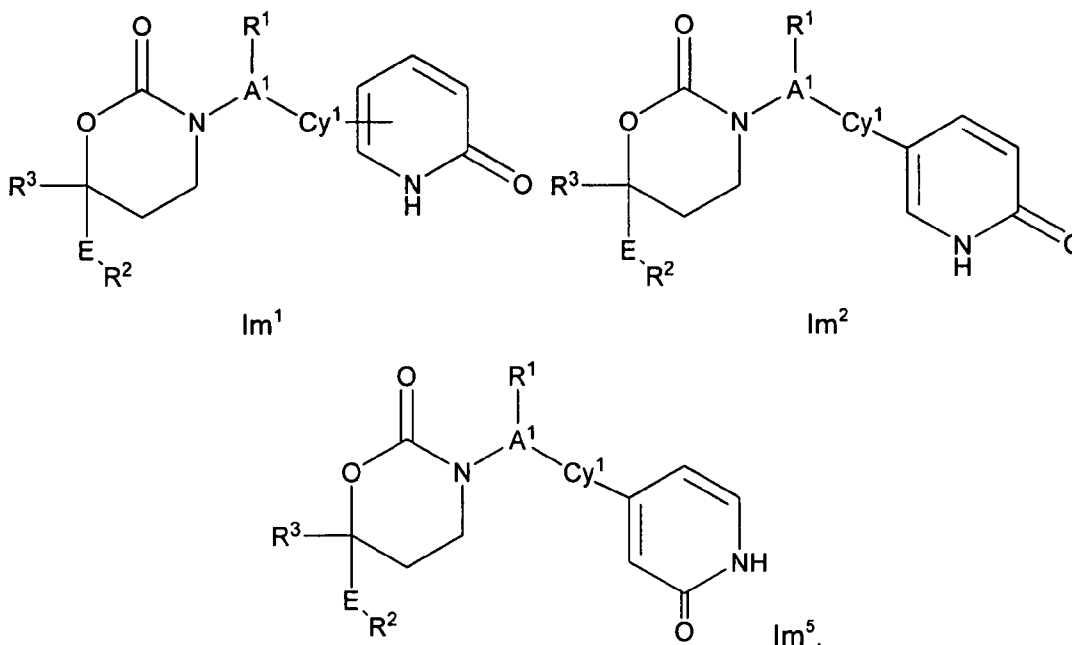
R^{1a} is absent or is methyl or ethyl;

- 5 Cy^2 is 2-oxo-1,2-dihydropyridyl optionally substituted by 1 to 4 groups independently selected from halo, hydroxy, methoxy, hydroxymethyl, methoxycarbonyl, amino, carbamoyl, methylcarbamoyl, dimethylcarbamoyl, (2-methoxyethyl)aminocarbonyl, acetylaminomethyl, methylsulfonyl, methylsulfonylamino, methylaminosulfonyl, isopropylaminosulfonyl, dimethylaminosulfonyl, pyrrolidine-1-sulfonyl, methylsulfonylaminomethyl, tetrazolyl, methyl, trifluoromethyl, acetyl, 2-hydroxyethyl and 1-aminoethyl;

R^2 is phenyl, thienyl, pyridyl or isopropyl each optionally substituted with halo, methyl, methylthio or (4-morpholino)methyl; and

- 15 R^3 is methyl, ethyl, propyl, butyl, vinyl, allyl or ethoxyethyl each optionally substituted with up to two groups independently selected from Methyl, HO-, MeO-, H_2N -, $MeC(=O)NH$ -, $MeS(=O)_2NH$ -, $H_2NC(=O)$ -, $MeNHC(=O)$ -, HO_2C -, $(HO)_2P(=O)O$ -, $H_2NS(=O)_2O$ -, $H_2NS(=O)_2NH$ -, $MeNHC(=O)NH$ -, $MeNHC(=O)O$ -, oxo, cyano, HO_2C -, $HOCH_2CH_2NH$ -, 4-morpholino, $HOCH_2C(=O)NH$ -, $H_2NCH_2C(=O)NH$ -, $EtNHC(=O)NH$ -, $MeOC(=O)NH$ -, $MeNHC(=NC\equiv N)NH$ -, Me-, MeS-, $MeSO_2$ -, $MeSO_2N(Me)$ -,
 20 $MeS(=O)_2NHC(=O)$ -, imidazolylamino-, imidazolyl, tetrazolyl, H_2NCONH -, H_2NCO_2 -, $HOCH_2CH_2O$ -, $MeNH$ -, Me_2N - and MeCONMe.

Another embodiment of the invention is a compound of any one of Formulas Im¹, Im² and Im⁵ or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof:

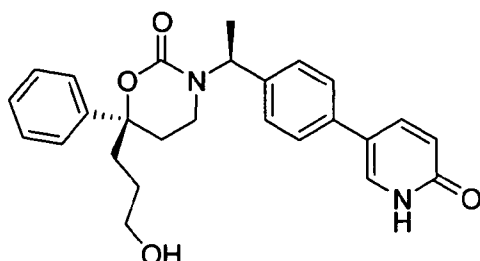


In Formulas Im^1 , Im^2 and Im^5 , the oxodihydropyridyl ring is optionally substituted

- 5 (substitution at ring carbons bonded to hydrogen and ring nitrogen atoms bonded to hydrogen atoms are encompassed, i.e., a "substitutable ring nitrogen atom") with up to four substituents as described above. Suitable substituents for the oxodihydropyridyl ring and suitable values for R^1 , R^2 , R^3 , A^1 , Cy^1 and E are as defined above in the first embodiment. Alternatively, suitable substituents for Cy^1 and the oxodihydropyridyl ring
- 10 in Formulas Im^1 , Im^2 and Im^5 are independently fluorine, chlorine, bromine, iodine, cyano, nitro, amino, hydroxy, carboxy, $(\text{C}_1\text{-C}_6)\text{alkyl}$, hydroxy $(\text{C}_1\text{-C}_6)\text{alkyl}$, $(\text{C}_3\text{-C}_6)\text{cycloalkyl}$, hydroxy $(\text{C}_3\text{-C}_6)\text{cycloalkyl}$, $(\text{C}_4\text{-C}_7)\text{cycloalkylalkyl}$, $(\text{C}_2\text{-C}_6)\text{alkenyl}$, halo $(\text{C}_2\text{-C}_6)\text{alkenyl}$, hydroxy $(\text{C}_2\text{-C}_6)\text{alkenyl}$, $(\text{C}_2\text{-C}_6)\text{alkynyl}$, $(\text{C}_3\text{-C}_6)\text{cycloalkyl}(\text{C}_2\text{-C}_4)\text{alkynyl}$, halo $(\text{C}_1\text{-C}_6)\text{alkyl}$, halo $(\text{C}_3\text{-C}_6)\text{cycloalkyl}$, halo $(\text{C}_4\text{-C}_7)\text{cycloalkylalkyl}$, $(\text{C}_1\text{-C}_6)\text{alkoxy}$, $(\text{C}_3\text{-C}_6)\text{cycloalkoxy}$, $(\text{C}_4\text{-C}_7)\text{cycloalkylalkoxy}$, halo $(\text{C}_1\text{-C}_6)\text{alkoxy}$, halo $(\text{C}_3\text{-C}_6)\text{cycloalkoxy}$, halo $(\text{C}_4\text{-C}_7)\text{cycloalkylalkoxy}$, $(\text{C}_1\text{-C}_6)\text{alkylthio}$, $(\text{C}_3\text{-C}_6)\text{cycloalkylthio}$, $(\text{C}_4\text{-C}_7)\text{cycloalkylalkylthio}$, halo $(\text{C}_1\text{-C}_6)\text{alkylthio}$, halo $(\text{C}_3\text{-C}_6)\text{cycloalkylthio}$, halo $(\text{C}_4\text{-C}_7)\text{cycloalkylalkylthio}$, $(\text{C}_1\text{-C}_6)\text{alkanesulfinyl}$, $(\text{C}_3\text{-C}_6)\text{cycloalkanesulfinyl}$, $(\text{C}_4\text{-C}_7)\text{cycloalkylalkanesulfinyl}$, halo $(\text{C}_1\text{-C}_6)\text{alkanesulfinyl}$, halo $(\text{C}_3\text{-C}_6)\text{cycloalkanesulfinyl}$, halo $(\text{C}_4\text{-C}_7)\text{cycloalkylalkanesulfinyl}$, $(\text{C}_1\text{-C}_6)\text{alkanesulfonyl}$, $(\text{C}_3\text{-C}_6)\text{cycloalkanesulfonyl}$, $(\text{C}_4\text{-C}_7)\text{cycloalkylalkanesulfonyl}$, halo $(\text{C}_1\text{-C}_6)\text{alkanesulfonyl}$, halo $(\text{C}_3\text{-C}_6)\text{cycloalkanesulfonyl}$, halo $(\text{C}_4\text{-C}_7)\text{cycloalkylalkanesulfonyl}$, $(\text{C}_1\text{-C}_6)\text{alkylamino}$, di $(\text{C}_1\text{-C}_6)\text{alkylamino}$, $(\text{C}_1\text{-C}_6)\text{alkoxy}(\text{C}_1\text{-C}_6)\text{alkoxy}$, halo $(\text{C}_1\text{-C}_6)\text{alkoxy}(\text{C}_1\text{-C}_6)\text{alkoxy}$, $(\text{C}_1\text{-C}_6)\text{alkoxycarbonyl}$, H_2NCO , H_2NSO_2 ,
- 20

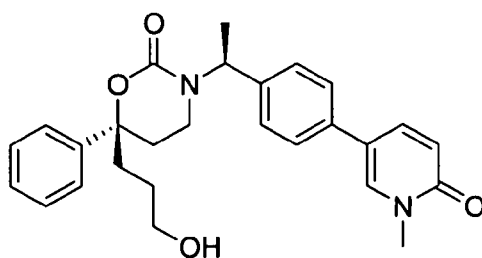
(C₁-C₆)alkylaminocarbonyl, di(C₁-C₆)alkylaminocarbonyl, (C₁-C₃)alkoxy(C₁-C₃)alkylaminocarbonyl, heterocyclylcarbonyl, (C₁-C₆)alkylaminosulfonyl, di(C₁-C₆)alkylaminosulfonyl, heterocyclosulfonyl, (C₁-C₆)alkylcarbonylamino, (C₁-C₆)alkylcarbonylamino(C₁-C₆)alkyl, (C₁-C₆)alkylsulfonylamino, (C₁-C₆)alkylsulfonylamino(C₁-C₆)alkyl, (C₁-C₆)alkoxy-carbonyl(C₁-C₆)alkoxy, (C₁-C₆)alkoxy(C₁-C₆)alkyl, halo(C₁-C₆)alkoxy(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkoxy, heteroaryl, amino(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)alkyl, di(C₁-C₆)alkylamino(C₁-C₆)alkyl amino(C₂-C₆)alkoxy, (C₁-C₆)alkylamino(C₂-C₆)alkoxy, di(C₁-C₆)alkylamino(C₂-C₆)alkoxy, (C₁-C₆)alkylcarbonyl, (C₃-C₆)cycloalkylcarbonyl, (C₃-C₆)cycloalkylaminocarbonyl, {(C₃-C₆)cycloalkyl}{(C₁-C₆)alkyl}aminocarbonyl, di(C₃-C₆)cycloalkylaminocarbonyl, (C₃-C₆)cycloalkylaminosulfonyl, {(C₃-C₆)cycloalkyl}{(C₁-C₆)alkyl}aminosulfonyl, di(C₃-C₆)cycloalkylaminosulfonyl, cyano(C₁-C₆)alkyl, aminocarbonyl(C₁-C₆)alkyl, (C₁-C₆)alkylaminocarbonyl(C₁-C₆)alkyl, di(C₁-C₆)alkylaminocarbonyl(C₁-C₆)alkyl, (C₃-C₆)cycloalkylaminocarbonyl(C₁-C₆)alkyl, {(C₃-C₆)cycloalkyl}{(C₁-C₆)alkyl}aminocarbonyl(C₁-C₆)alkyl and di(C₃-C₆)cycloalkylaminocarbonyl(C₁-C₆)alkyl;; and values for R¹, R², R³, A¹, Cy¹ and E are as defined above in the first embodiment. Alternatively, suitable substituents for Cy¹ include (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkyl, (C₁-C₄)haloalkoxy, halogen, cyano and nitro; suitable substituents for a substitutable ring nitrogen atom in the oxodihydropyridyl ring in Formulas Im¹, Im² and Im⁵ include (C₁-C₄)alkyl, (C₃-C₄)cycloalkyl, (C₃-C₄)cycloalkyl(C₁-C₂)alkyl, and (C₁-C₄)haloalkyl; suitable substituents for a ring carbon atom in the oxodihydropyridyl ring in Formulas Im¹, Im² and Im⁵ include fluorine, chlorine, cyano, hydroxy, amino, (C₁-C₄)alkyl, (C₃-C₄)cycloalkyl, (C₃-C₄)cycloalkyl(C₁-C₂)alkyl, halo(C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkoxy, CONH₂, (C₁-C₄)alkylaminocarbonyl, di(C₁-C₄)alkylaminocarbonyl and (C₁-C₄)alkylcarbonylamino; and suitable values for R¹, R², R³, A¹, Cy¹ and E are as defined above in the first embodiment. In another alternative, the embodiments in this paragraph exclude the following compounds:

(R)-6-(3-hydroxypropyl)-3-((S)-1-(4-(6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one



(PR-221); and

(R)-6-(3-hydroxypropyl)-3-((S)-1-(4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one



(PR-313);

5 or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

For each of the embodiments described in the previous paragraph, R¹ is preferably methyl or ethyl.

For each of the embodiments described in the paragraph immediately following Formulas Im¹, Im² and Im⁵, R¹ is preferably methyl or ethyl; and R³ is

10 MeSO₂NHCH₂CH₂CH₂, H₂NC(=O)CH₂CH₂, H₂NC(=O)CMe₂CH₂, 3-hydroxypropyl, 3-hydroxy-3-methylbutyl, 2-hydroxyethyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

For each of the embodiments described in the paragraph immediately following Formulas Im¹, Im² and Im⁵, R¹ is preferably methyl or ethyl; and R³ is

15 H₂NC(=O)CMe₂CH₂, 3-hydroxy-3-methylbutyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

For each of the embodiments described in the paragraph immediately following Formulas Im¹, Im² and Im⁵, R¹ is preferably methyl or ethyl; R² is phenyl optionally substituted with 1, 2 or 3 substituents selected from halo, cyano, CONH₂, (C₁-C₄)alkyl,

20 (C₁-C₄)haloalkyl, and SO₂Me; and R³ is MeSO₂NHCH₂CH₂CH₂, H₂NC(=O)CH₂CH₂,

H₂NC(=O)CMe₂CH₂, 3-hydroxypropyl, 3-hydroxy-3-methylbutyl, 2-hydroxyethyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

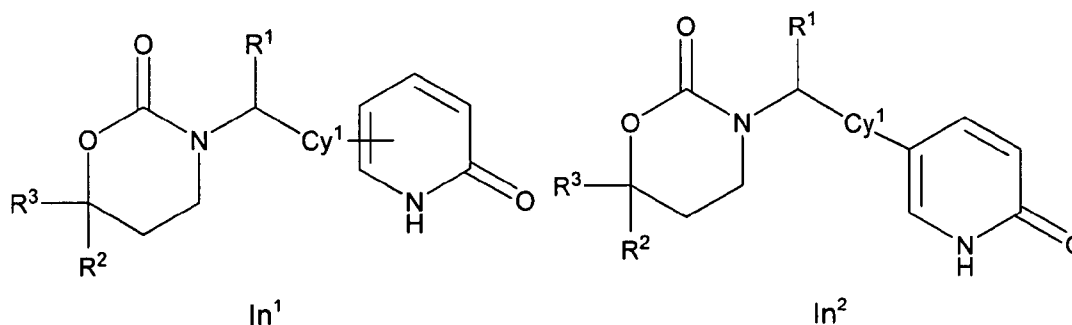
For each of the embodiments described in the paragraph immediately following Formulas Im¹, Im² and Im⁵, R¹ is preferably methyl or ethyl; R² is phenyl optionally substituted with 1, 2 or 3 substituents selected from halo, cyano, CONH₂, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl, and SO₂Me; and R³ is H₂NC(=O)CMe₂CH₂, 3-hydroxy-3-methylbutyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

For each of the embodiments described in the paragraph immediately following Formulas Im¹, Im² and Im⁵, R¹ is preferably methyl or ethyl; and R³ is 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

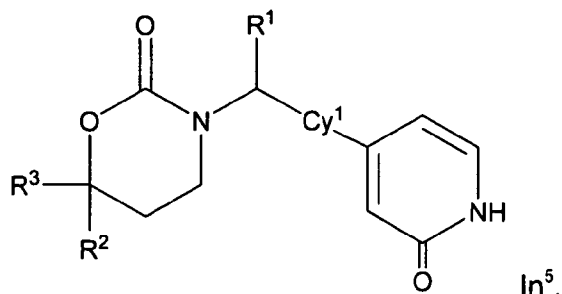
For each of the embodiments described in the paragraph immediately following Formulas Im¹, Im² and Im⁵, R¹ is preferably methyl or ethyl; R² is phenyl or fluorophenyl; and R³ is 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

For each of the embodiments described in the paragraph immediately following Formulas Im¹, Im² and Im⁵, R¹ is preferably methyl or ethyl; R² is phenyl or fluorophenyl; R³ is 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl; the substituent on the substitutable ring nitrogen atom in the oxodihydropyridyl ring in Formulas Im¹, Im² and Im⁵ is (C₁-C₄)alkyl, (C₃-C₄)cycloalkyl, (C₃-C₄)cycloalkyl(C₁-C₂)alkyl, or (C₁-C₂)haloalkyl; and one or two ring carbon atoms in the oxodihydropyridyl ring in Formulas Im¹, Im² and Im⁵ are optionally substituted with methyl or ethyl.

Another embodiment of the invention is a compound of any one of Formulas In¹, In² and In⁵, or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof:



- 17 -



In Formulas In¹, In² and In⁵, the oxodihydropyridyl ring is optionally substituted (substitution at ring carbons bonded to hydrogen and at nitrogen atoms bonded to hydrogen atoms are encompassed, i.e., a "substitutable ring nitrogen atom") with up to four substituents as described above for Cy². Suitable substituents for the oxodihydropyridyl ring and suitable values for R¹, R², R³ and Cy¹ are as defined above in the first embodiment. Alternatively, suitable substituents for Cy¹ and the oxodihydropyridyl ring in Formulas In¹, In² and In⁵ are independently fluorine, chlorine, bromine, iodine, cyano, nitro, amino, hydroxy, carboxy, (C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, hydroxy(C₃-C₆)cycloalkyl, (C₄-C₇)cycloalkylalkyl, (C₂-C₆)alkenyl, halo(C₂-C₆)alkenyl, hydroxy(C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₆)cycloalkyl(C₂-C₄)alkynyl, halo(C₁-C₆)alkyl, halo(C₃-C₆)cycloalkyl, halo(C₄-C₇)cycloalkylalkyl, (C₁-C₆)alkoxy, (C₃-C₆)cycloalkoxy, (C₄-C₇)cycloalkylalkoxy, halo(C₁-C₆)alkoxy, halo(C₃-C₆)cycloalkoxy, halo(C₄-C₇)cycloalkylalkoxy, (C₁-C₆)alkylthio, (C₃-C₆)cycloalkylthio, (C₄-C₇)cycloalkylalkylthio, halo(C₁-C₆)alkylthio, halo(C₃-C₆)cycloalkylthio, halo(C₄-C₇)cycloalkylalkylthio, (C₁-C₆)alkanesulfinyl, (C₃-C₆)cycloalkanesulfinyl, (C₄-C₇)cycloalkylalkanesulfinyl, halo(C₁-C₆)alkanesulfinyl, halo(C₃-C₆)cycloalkanesulfinyl, halo(C₄-C₇)cycloalkylalkanesulfinyl, (C₁-C₆)alkanesulfonyl, (C₃-C₆)cycloalkanesulfonyl, (C₄-C₇)cycloalkylalkanesulfonyl, halo(C₁-C₆)alkanesulfonyl, halo(C₃-C₆)cycloalkanesulfonyl, halo(C₄-C₇)cycloalkylalkanesulfonyl, (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, (C₁-C₆)alkoxy(C₁-C₆)alkoxy, halo(C₁-C₆)alkoxy(C₁-C₆)alkoxy, (C₁-C₆)alkoxycarbonyl, H₂NCO, H₂NSO₂, (C₁-C₆)alkylaminocarbonyl, di(C₁-C₆)alkylaminocarbonyl, (C₁-C₃)alkoxy(C₁-C₃)alkylaminocarbonyl, heterocyclylcarbonyl, (C₁-C₆)alkylaminosulfonyl, di(C₁-C₆)alkylaminosulfonyl, heterocyclosulfonyl, (C₁-C₆)alkylcarbonylamino, (C₁-C₆)alkylcarbonylamino(C₁-C₆)alkyl, (C₁-C₆)alkylsulfonylamino, (C₁-C₆)alkylsulfonylamino(C₁-C₆)alkyl, (C₁-C₆)alkoxycarbonyl(C₁-C₆)alkoxy, (C₁-C₆)alkoxy(C₁-C₆)alkyl, halo(C₁-C₆)alkoxy(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkoxy, heteroaryl, amino(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)alkyl, di(C₁-

C_6 alkylamino(C_1 - C_6)alkyl amino(C_2 - C_6)alkoxy, (C_1 - C_6)alkylamino(C_2 - C_6)alkoxy, di(C_1 - C_6)alkylamino(C_2 - C_6)alkoxy, (C_1 - C_6)alkylcarbonyl, (C_3 - C_6)cycloalkylcarbonyl, (C_3 - C_6)cycloalkylaminocarbonyl, $\{(C_3$ - C_6)cycloalkyl $\}(C_1$ - C_6)alkylaminocarbonyl, di(C_3 - C_6)cycloalkylaminocarbonyl, (C_3 - C_6)cycloalkylaminosulfonyl, $\{(C_3$ - C_6)cycloalkyl $\}(C_1$ - C_6)alkylaminosulfonyl, di(C_3 - C_6)cycloalkylaminosulfonyl, cyano(C_1 - C_6)alkyl, aminocarbonyl(C_1 - C_6)alkyl, (C_1 - C_6)alkylaminocarbonyl(C_1 - C_6)alkyl, di(C_1 - C_6)alkylaminocarbonyl(C_1 - C_6)alkyl, (C_3 - C_6)cycloalkylaminocarbonyl(C_1 - C_6)alkyl, $\{(C_3$ - C_6)cycloalkyl $\}(C_1$ - C_6)alkylaminocarbonyl(C_1 - C_6)alkyl and di(C_3 - C_6)cycloalkylaminocarbonyl(C_1 - C_6)alkyl; and values for R^1 , R^2 , R^3 and Cy^1 are as defined above in the first embodiment. Alternatively, suitable substituents for Cy^1 include (C_1 - C_4)alkyl, (C_1 - C_4)alkoxy, (C_1 - C_4)haloalkyl, (C_1 - C_4)haloalkoxy, halogen, cyano and nitro; suitable substituents for a substitutable ring nitrogen atom in the oxodihydropyridyl ring in Formulas In^1 , In^2 and In^5 include (C_1 - C_4)alkyl, (C_3 - C_4)cycloalkyl, (C_3 - C_4)cycloalkyl(C_1 - C_2)alkyl and (C_1 - C_4)haloalkyl; suitable substituents for a ring carbon atom in the oxodihydropyridyl ring in Formulas In^1 , In^2 and In^5 include fluorine, chlorine, cyano, hydroxy, amino, (C_1 - C_4)alkyl, (C_3 - C_4)cycloalkyl, (C_3 - C_4)cycloalkyl(C_1 - C_2)alkyl, halo(C_1 - C_4)alkyl, (C_1 - C_4)alkoxy, (C_1 - C_4)haloalkoxy, $CONH_2$, (C_1 - C_4)alkylaminocarbonyl, di(C_1 - C_4)alkylaminocarbonyl and (C_1 - C_4)alkylcarbonylamino; and suitable values for R^1 , R^2 , R^3 , and Cy^1 are as defined above in the first embodiment. In another alternative, the embodiments described in this paragraph exclude the compounds PR-221 and PR-313; or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

For each of the embodiments described in the previous paragraph, R^1 is preferably methyl or ethyl.

For each of the embodiments described in the paragraph immediately following Formulas In^1 , In^2 and In^5 , R^1 is preferably methyl or ethyl; and R^3 is $MeSO_2NHCH_2CH_2CH_2$, $H_2NC(=O)CH_2CH_2$, $H_2NC(=O)CMe_2CH_2$, 3-hydroxypropyl, 3-hydroxy-3-methylbutyl, 2-hydroxyethyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

For each of the embodiments described in the paragraph immediately following Formulas In^1 , In^2 and In^5 , R^1 is preferably methyl or ethyl; and R^3 is $H_2NC(=O)CMe_2CH_2$, 3-hydroxy-3-methylbutyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

For each of the embodiments described in the paragraph immediately following Formulas In^1 , In^2 and In^5 , R^1 is preferably methyl or ethyl; R^2 is phenyl optionally

substituted with 1, 2 or 3 substituents selected from halo, cyano, CONH_2 , $(\text{C}_1\text{-C}_4)\text{alkyl}$, $(\text{C}_1\text{-C}_4)\text{haloalkyl}$ and SO_2Me ; and R^3 is $\text{MeSO}_2\text{NHCH}_2\text{CH}_2\text{CH}_2$, $\text{H}_2\text{NC(=O)CH}_2\text{CH}_2$, $\text{H}_2\text{NC(=O)CMe}_2\text{CH}_2$, 3-hydroxypropyl, 3-hydroxy-3-methylbutyl, 2-hydroxyethyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

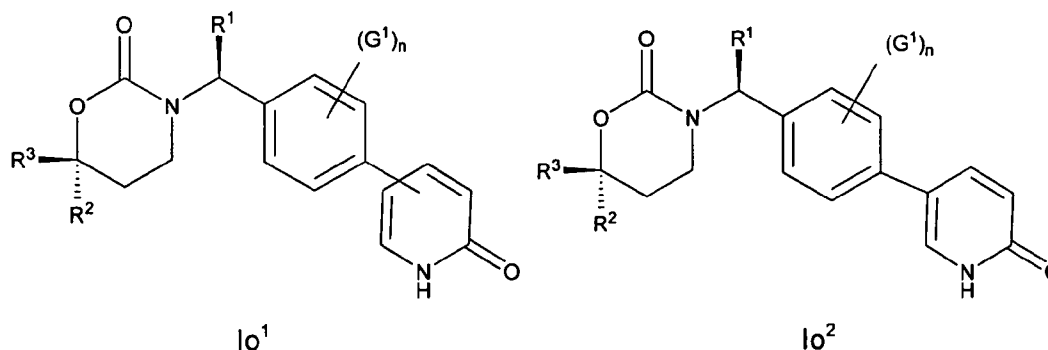
5 For each of the embodiments described in the paragraph immediately following Formulas In^1 , In^2 and In^5 , R^1 is preferably methyl or ethyl; R^2 is phenyl optionally substituted with 1, 2 or 3 substituents selected from halo, cyano, CONH_2 , $(\text{C}_1\text{-C}_4)\text{alkyl}$, $(\text{C}_1\text{-C}_4)\text{haloalkyl}$ and SO_2Me ; and R^3 is $\text{H}_2\text{NC(=O)CMe}_2\text{CH}_2$, 3-hydroxy-3-methylbutyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

10 For each of the embodiments described in the paragraph immediately following Formulas In^1 , In^2 and In^5 , R^1 is preferably methyl or ethyl; and R^3 is 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

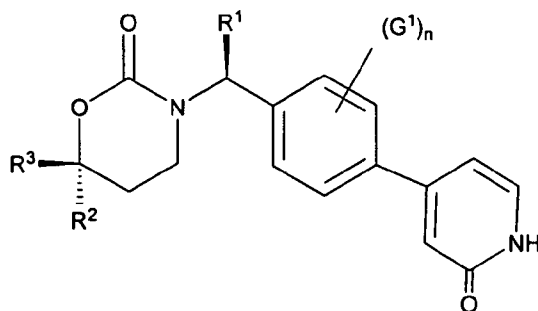
For each of the embodiments described in the paragraph immediately following Formulas In^1 , In^2 and In^5 , R^1 is preferably methyl or ethyl; R^2 is phenyl or fluorophenyl; and R^3 is 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

For each of the embodiments described in the paragraph immediately following Formulas In^1 , In^2 and In^5 , R^1 is preferably methyl or ethyl; R^2 is phenyl or fluorophenyl; R^3 is 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl; the substituent on the substitutable ring nitrogen atom in the oxodihydropyridyl rings in Formulas In^1 , In^2 and In^5 is $(\text{C}_1\text{-C}_4)\text{alkyl}$, $(\text{C}_3\text{-C}_4)\text{cycloalkyl}$, $(\text{C}_3\text{-C}_4)\text{cycloalkyl}(\text{C}_1\text{-C}_2)\text{alkyl}$, or $(\text{C}_1\text{-C}_2)\text{haloalkyl}$; and one or two ring carbon atoms in the oxodihydropyridyl rings in Formulas In^1 , In^2 and In^5 are optionally substituted with methyl or ethyl.

Another embodiment of the invention is a compound of any one of Formulas Io^1 , Io^2 and Io^5 , or a pharmaceutically acceptable salt thereof:



- 20 -

10⁵.

In Formulas 10¹, 10² and 10⁵, the oxodihydropyridyl ring in Formulas 10¹, 10² and 10⁵ is optionally substituted (substitution at ring carbons bonded to hydrogen and at nitrogen atoms bonded to hydrogen atoms are encompassed, i.e., a "substitutable ring nitrogen atom") with up to four substituents as described above in the first embodiment; suitable values for G¹ are fluorine, chlorine, bromine, iodine, cyano, nitro, amino, hydroxy, carboxy, (C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, hydroxy(C₃-C₆)cycloalkyl, (C₄-C₇)cycloalkylalkyl, (C₂-C₆)alkenyl, halo(C₂-C₆)alkenyl, hydroxy(C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₆)cycloalkyl(C₂-C₄)alkynyl, halo(C₁-C₆)alkyl, halo(C₃-C₆)cycloalkyl, halo(C₄-C₇)cycloalkylalkyl, (C₁-C₆)alkoxy, (C₃-C₆)cycloalkoxy, (C₄-C₇)cycloalkylalkoxy, halo(C₁-C₆)alkoxy, halo(C₃-C₆)cycloalkoxy, halo(C₄-C₇)cycloalkylalkoxy, (C₁-C₆)alkylthio, (C₃-C₆)cycloalkylthio, (C₄-C₇)cycloalkylalkylthio, halo(C₁-C₆)alkylthio, halo(C₃-C₆)cycloalkylthio, halo(C₄-C₇)cycloalkylalkylthio, (C₁-C₆)alkanesulfinyl, (C₃-C₆)cycloalkanesulfinyl, (C₄-C₇)cycloalkylalkanesulfinyl, halo(C₁-C₆)alkanesulfinyl, halo(C₃-C₆)cycloalkanesulfinyl, halo(C₄-C₇)cycloalkylalkanesulfinyl, (C₁-C₆)alkanesulfonyl, (C₃-C₆)cycloalkanesulfonyl, (C₄-C₇)cycloalkylalkanesulfonyl, halo(C₁-C₆)alkanesulfonyl, halo(C₃-C₆)cycloalkanesulfonyl, halo(C₄-C₇)cycloalkylalkanesulfonyl, (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, (C₁-C₆)alkoxy(C₁-C₆)alkoxy, halo(C₁-C₆)alkoxy(C₁-C₆)alkoxy, (C₁-C₆)alkoxycarbonyl, H₂NCO, H₂NSO₂, (C₁-C₆)alkylaminocarbonyl, di(C₁-C₆)alkylaminocarbonyl, (C₁-C₃)alkoxy(C₁-C₃)alkylaminocarbonyl, heterocyclylcarbonyl, (C₁-C₆)alkylaminosulfonyl, di(C₁-C₆)alkylaminosulfonyl, heterocyclosulfonyl, (C₁-C₆)alkylcarbonylamino, (C₁-C₆)alkylcarbonylamino(C₁-C₆)alkyl, (C₁-C₆)alkylsulfonylamino, (C₁-C₆)alkylsulfonylamino(C₁-C₆)alkyl, (C₁-C₆)alkoxycarbonyl(C₁-C₆)alkoxy, (C₁-C₆)alkoxy(C₁-C₆)alkyl, halo(C₁-C₆)alkoxy(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkoxy, heteroaryl, amino(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)alkyl, di(C₁-C₆)alkylamino(C₁-C₆)alkyl amino(C₂-C₆)alkoxy, (C₁-C₆)alkylamino(C₂-C₆)alkoxy,

di(C₁-C₆)alkylamino(C₂-C₆)alkoxy, (C₁-C₆)alkylcarbonyl, (C₃-C₆)cycloalkylcarbonyl, (C₃-C₆)cycloalkylaminocarbonyl, {(C₃-C₆)cycloalkyl}{(C₁-C₆)alkyl}aminocarbonyl, di(C₃-C₆)cycloalkylaminocarbonyl, (C₃-C₆)cycloalkylaminosulfonyl, {(C₃-C₆)cycloalkyl}{(C₁-C₆)alkyl}aminosulfonyl, di(C₃-C₆)cycloalkylaminosulfonyl, cyano(C₁-C₆)alkyl,

5 aminocarbonyl(C₁-C₆)alkyl, (C₁-C₆)alkylaminocarbonyl(C₁-C₆)alkyl, di(C₁-C₆)alkylaminocarbonyl(C₁-C₆)alkyl, (C₃-C₆)cycloalkylaminocarbonyl(C₁-C₆)alkyl, {(C₃-C₆)cycloalkyl}{(C₁-C₆)alkyl}aminocarbonyl(C₁-C₆)alkyl and di(C₃-C₆)cycloalkylaminocarbonyl(C₁-C₆)alkyl; n is 0, 1, 2 or 3; and suitable substituents for the

10 oxodihydropyridyl ring and suitable values for R¹, R² and R³ are as defined above in the first embodiment. Alternatively, n is 0, 1, 2 or 3; suitable values for G¹ and substituents for the oxodihydropyridyl ring in Formulas Io¹, Io² and Io⁵ are independently fluorine, chlorine, bromine, iodine, cyano, nitro, amino, hydroxy, carboxy, (C₁-C₆)alkyl,

hydroxy(C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, hydroxy(C₃-C₆)cycloalkyl, (C₄-C₇)cycloalkylalkyl, (C₂-C₆)alkenyl, halo(C₂-C₆)alkenyl, hydroxy(C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₃-C₆)cycloalkyl(C₂-C₄)alkynyl, halo(C₁-C₆)alkyl, halo(C₃-C₆)cycloalkyl, halo(C₄-C₇)cycloalkylalkyl, (C₁-C₆)alkoxy, (C₃-C₆)cycloalkoxy, (C₄-C₇)cycloalkylalkoxy, halo(C₁-C₆)alkoxy, halo(C₃-C₆)cycloalkoxy, halo(C₄-C₇)cycloalkylalkoxy, (C₁-C₆)alkylthio, (C₃-C₆)cycloalkylthio, (C₄-C₇)cycloalkylalkylthio, halo(C₁-C₆)alkylthio, halo(C₃-C₆)cycloalkylthio, halo(C₄-C₇)cycloalkylalkylthio, (C₁-C₆)alkanesulfinyl, (C₃-C₆)cycloalkanesulfinyl, (C₄-C₇)cycloalkylalkanesulfinyl, halo(C₁-C₆)alkanesulfinyl, halo(C₃-C₆)cycloalkanesulfinyl, halo(C₄-C₇)cycloalkylalkanesulfinyl, (C₁-C₆)alkanesulfonyl, (C₃-C₆)cycloalkanesulfonyl, (C₄-C₇)cycloalkylalkanesulfonyl, halo(C₁-C₆)alkanesulfonyl, halo(C₃-C₆)cycloalkanesulfonyl, halo(C₄-C₇)cycloalkylalkanesulfonyl, (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, (C₁-C₆)alkoxy(C₁-C₆)alkoxy, halo(C₁-C₆)alkoxy(C₁-C₆)alkoxy, (C₁-C₆)alkoxycarbonyl, H₂NCO, H₂NSO₂, (C₁-C₆)alkylaminocarbonyl, di(C₁-C₆)alkylaminocarbonyl, (C₁-C₃)alkoxy(C₁-C₃)alkylaminocarbonyl, heterocyclylcarbonyl, (C₁-C₆)alkylaminosulfonyl, di(C₁-C₆)alkylaminosulfonyl, heterocyclosulfonyl, (C₁-C₆)alkylcarbonylamino, (C₁-C₆)alkylcarbonylamino(C₁-C₆)alkyl, (C₁-C₆)alkylsulfonylamino, (C₁-C₆)alkylsulfonylamino(C₁-C₆)alkyl, (C₁-C₆)alkoxycarbonyl(C₁-C₆)alkoxy, (C₁-C₆)alkoxy(C₁-C₆)alkyl, halo(C₁-C₆)alkoxy(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkoxy, heteroaryl, amino(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)alkyl, di(C₁-C₆)alkylamino(C₁-C₆)alkyl amino(C₂-C₆)alkoxy, (C₁-C₆)alkylamino(C₂-C₆)alkoxy, di(C₁-C₆)alkylamino(C₂-C₆)alkoxy and (C₁-C₆)alkylcarbonyl; and values for R¹, R² and R³

are as defined above in the first embodiment. Alternatively, n is 0, 1, 2 or 3; suitable values for G¹ include (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkyl, (C₁-C₄)haloalkoxy, halogen, cyano and nitro; suitable substituents for a substitutable ring nitrogen atom in the oxodihydropyridyl ring in Formulas Io¹, Io² and Io⁵ include C₁-C₄ alkyl, (C₃-C₄)cycloalkyl, (C₃-C₄)cycloalkyl(C₁-C₂)alkyl and C₁-C₄ haloalkyl; suitable substituents for a ring carbon atom in the oxodihydropyridyl ring in Formulas Io¹, Io² and Io⁵ include fluorine, chlorine, cyano, hydroxy, amino, (C₁-C₄)alkyl, (C₃-C₄)cycloalkyl, (C₃-C₄)cycloalkyl(C₁-C₂)alkyl, halo(C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkoxy, CONH₂, (C₁-C₄)alkylaminocarbonyl, di(C₁-C₄)alkylaminocarbonyl and (C₁-C₄)alkylcarbonylamino; and suitable values for R¹, R² and R³ are as defined above in the first embodiment. In another alternative, the embodiments described in this paragraph exclude the compounds PR-221 and PR-313; or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

For each of the embodiments described in the previous paragraph, R¹ is preferably methyl or ethyl.

For each of the embodiments described in the paragraph immediately following Formulas Io¹, Io² and Io⁵, R¹ is preferably methyl or ethyl; and R³ is MeSO₂NHCH₂CH₂CH₂, H₂NC(=O)CH₂CH₂, H₂NC(=O)CMe₂CH₂, 3-hydroxypropyl, 3-hydroxy-3-methylbutyl, 2-hydroxyethyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

For each of the embodiments described in the paragraph immediately following Formulas Io¹, Io² and Io⁵, R¹ is preferably methyl or ethyl; and R³ is H₂NC(=O)CMe₂CH₂, 3-hydroxy-3-methylbutyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

For each of the embodiments described in the paragraph immediately following Formulas Io¹, Io² and Io⁵, R¹ is preferably methyl or ethyl; R² is phenyl optionally substituted with 1, 2 or 3 substituents selected from halo, cyano, CONH₂, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl and SO₂Me; and R³ is MeSO₂NHCH₂CH₂CH₂, H₂NC(=O)CH₂CH₂, H₂NC(=O)CMe₂CH₂, 3-hydroxypropyl, 3-hydroxy-3-methylbutyl, 2-hydroxyethyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

For each of the embodiments described in the paragraph immediately following Formulas Io¹, Io² and Io⁵, R¹ is preferably methyl or ethyl; R² is phenyl optionally substituted with 1, 2 or 3 substituents selected from halo, cyano, CONH₂, (C₁-C₄)alkyl,

(C₁-C₄)haloalkyl and SO₂Me; and R³ is H₂NC(=O)CMe₂CH₂, 3-hydroxy-3-methylbutyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

For each of the embodiments described in the paragraph immediately following Formulas Io¹, Io² and Io⁵, R¹ is preferably methyl or ethyl; and R³ is 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

For each of the embodiments described in the paragraph immediately following Formulas Io¹, Io² and Io⁵, R¹ is preferably methyl or ethyl; R² is phenyl or fluorophenyl; and R³ is 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

For each of the embodiments described in the paragraph immediately following Formulas Io¹, Io² and Io⁵, R¹ is preferably methyl or ethyl; R² is phenyl or fluorophenyl; R³ is 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl; the substituent on the substitutable ring nitrogen atom in the oxodihydropyridyl ring in Formulas Io¹, Io² and Io⁵ is (C₁-C₄)alkyl, (C₃-C₄)cycloalkyl, (C₃-C₄)cycloalkyl(C₁-C₂)alkyl, or (C₁-C₂)haloalkyl; and one or two ring carbon atoms in the oxodihydropyridyl rings in Formulas Io¹, Io² and Io⁵ are optionally substituted with methyl or ethyl.

Another embodiment of the invention (referred to herein as the "First Alternate Embodiment") is a compound represented by Structural Formulas Io¹, Io² and Io⁵, wherein: n is 0 or 1, preferably 0; each G¹ is independently (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkyl, (C₁-C₄)haloalkoxy, halogen, cyano or nitro; the oxodihydropyridyl is substituted at its ring nitrogen atom with hydroxy(C₁-C₆)alkyl, (C₁-C₆)alkyl-carbonylamino(C₁-C₆)alkyl, (C₁-C₆)alkylsulfonylamino(C₁-C₆)alkyl, (C₁-C₆)alkoxy(C₁-C₆)alkyl, amino(C₁-C₆)alkyl, (C₁-C₆)alkylamino(C₁-C₆)alkyl, di(C₁-C₆)alkylamino(C₁-C₆)alkyl, cyano(C₁-C₆)alkyl, aminocarbonyl(C₁-C₆)alkyl, (C₁-C₆)alkylaminocarbonyl(C₁-C₆)alkyl, di(C₁-C₆)alkylaminocarbonyl(C₁-C₆)alkyl, (C₃-C₆)cycloalkylaminocarbonyl(C₁-C₆)alkyl, {(C₃-C₆)cycloalkyl}{(C₁-C₆)alkyl}aminocarbonyl(C₁-C₆)alkyl or di(C₃-C₆)cycloalkylaminocarbonyl(C₁-C₆)alkyl; the oxodihydropyridyl is optionally substituted at one or more substitutable ring carbon atoms with a group independently selected from fluorine, chlorine, cyano, hydroxy, amino, (C₁-C₄)alkyl, (C₃-C₄)cycloalkyl, (C₃-C₄)cycloalkyl(C₁-C₂)alkyl, halo(C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkoxy, CONH₂, (C₁-C₄)alkylaminocarbonyl, di(C₁-C₄)alkylaminocarbonyl and (C₁-C₄)alkylcarbonylamino; R¹ is methyl or ethyl; R² is phenyl, thienyl, pyridyl or isopropyl each optionally substituted with up to three groups independently selected from halo, methyl, methylthio, (4-morpholino)methyl or cyclopropyl; and R³ is methyl, ethyl, propyl, butyl, vinyl, allyl or

ethoxyethyl each optionally substituted with up to two groups independently selected from methyl, HO-, MeO-, H₂N-, MeC(=O)NH-, MeS(=O)₂NH-, H₂NC(=O)-, MeNHC(=O)-, HO₂C-, (HO)₂P(=O)O-, H₂NS(=O)₂O-, H₂NS(=O)₂NH-, MeNHC(=O)NH-, MeNHC(=O)O-, oxo, cyano, HO₂C-, HOCH₂CH₂NH-, 4-morpholino, HOCH₂C(=O)NH-, H₂NCH₂C(=O)NH-
 5 , EtNHC(=O)NH, MeOC(=O)NH-, MeNHC(=NC≡N)NH-, Me-, MeS-, MeSO₂-
 MeSO₂N(Me)-, MeS(=O)₂NHC(=O)-, imidazolylamino-, imidazolyl, tetrazolyl, H₂NCONH-, H₂NCO₂-, HOCH₂CH₂O-, MeNH-, Me₂N- and MeCONMe.

Alternatively for Structural Formulas Io¹, Io² and Io⁵, R² is phenyl optionally substituted with 1, 2 or 3 substituents independently selected from halo, cyano, CONH₂,
 10 (C₁-C₄)alkyl, (C₁-C₄)haloalkyl and SO₂Me; and R³ is is MeSO₂NHCH₂CH₂CH₂,
 H₂NC(=O)CH₂CH₂, H₂NC(=O)CMe₂CH₂, 3-hydroxypropyl, 3-hydroxy-3-methylbutyl, 2-hydroxyethyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl; and the remainder of the variables are as described above for the First Alternate Embodiment.

Alternatively for Structural Formulas Io¹, Io² and Io⁵, R³ is H₂NC(=O)CMe₂CH₂, 3-
 15 hydroxy-3-methylbutyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl; and the remainder of the variables are as described above for the First Alternate Embodiment.

Alternatively for Structural Formulas Io¹, Io² and Io⁵, R² is phenyl optionally substituted with 1, 2 or 3 substituents independently selected from halo, cyano, CONH₂, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl and SO₂Me; and R³ is H₂NC(=O)CMe₂CH₂, 3-hydroxy-3-
 20 methylbutyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl; and the remainder of the variables are as described in the First Alternate Embodiment.

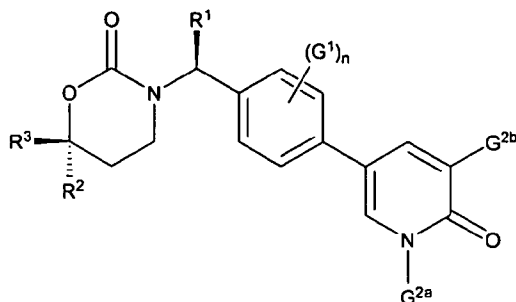
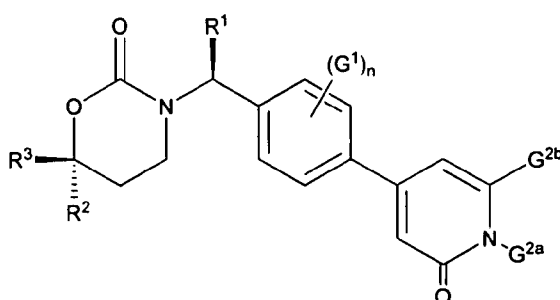
Alternatively for Structural Formulas Io¹, Io² and Io⁵, R³ is 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl; and the remainder of the variables are as described in the First Alternate Embodiment.

Alternatively for Structural Formulas Io¹, Io² and Io⁵, R² is phenyl or fluorophenyl; and R³ is 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl; and the remainder of the variables are as described in the First Alternate Embodiment.

Alternatively for Structural Formulas Io¹, Io² and Io⁵, R² is phenyl or fluorophenyl; R³ is 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl; one or two ring
 30 carbon atoms in the oxodihydropyridyl rings are optionally substituted with fluorine, methyl or ethyl; and the remainder of the variables are as described in the First Alternate Embodiment.

For the embodiment described in the previous seven paragraphs, n is 0 and all of the substitutable ring carbons in the oxodihydropyridyl are preferably unsubstituted.

Another embodiment of the invention is a compound represented by any one of Formulas Ip¹ and Ip³, or a pharmaceutically acceptable salt thereof:

Ip¹Ip³.

In Formulas Ip¹ and Ip³, G¹ is (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkyl, (C₁-C₄)haloalkoxy, halogen, cyano or nitro; n is 0, 1 or 2; G^{2a} is (C₁-C₄)alkyl, (C₃-C₄)cycloalkyl or (C₁-C₄)haloalkyl; G^{2b} is hydrogen, fluorine, chlorine, cyano, hydroxy, amino, (C₁-C₄)alkyl, (C₃-C₄)cycloalkyl, (C₃-C₄)cycloalkyl(C₁-C₂)alkyl, halo(C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)haloalkoxy, CONH₂, (C₁-C₄)alkylaminocarbonyl, di(C₁-C₄)alkylaminocarbonyl or (C₁-C₄)alkylcarbonylamino; and suitable values for R¹, R² and R³ are as defined above in the first embodiment. In another alternative, the embodiments described in this paragraph exclude the compounds PR-221 and PR-313; or a pharmaceutically acceptable salt, enantiomer or diastereomer thereof.

For each of the embodiments described in the previous paragraph, R¹ is preferably methyl or ethyl.

For each of the embodiments described in the paragraph immediately following Formulas Ip¹ and Ip³, R¹ is preferably methyl or ethyl; and R³ is MeSO₂NHCH₂CH₂CH₂,

$\text{H}_2\text{NC}(=\text{O})\text{CH}_2\text{CH}_2$, $\text{H}_2\text{NC}(=\text{O})\text{CMe}_2\text{CH}_2$, 3-hydroxypropyl, 3-hydroxy-3-methylbutyl, 2-hydroxyethyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

For each of the embodiments described in the paragraph immediately following Formulas Ip¹ and Ip³, R¹ is preferably methyl or ethyl; and R³ is $\text{H}_2\text{NC}(=\text{O})\text{CMe}_2\text{CH}_2$, 3-hydroxy-3-methylbutyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

For each of the embodiments described in the paragraph immediately following Formulas Ip¹ and Ip³, R¹ is preferably methyl or ethyl; R² is phenyl optionally substituted with 1, 2 or 3 substituents selected from halo, cyano, CONH_2 , (C₁-C₄)alkyl, (C₁-C₄)haloalkyl and SO_2Me ; and R³ is $\text{MeSO}_2\text{NHCH}_2\text{CH}_2\text{CH}_2$, $\text{H}_2\text{NC}(=\text{O})\text{CH}_2\text{CH}_2$, $\text{H}_2\text{NC}(=\text{O})\text{CMe}_2\text{CH}_2$, 3-hydroxypropyl, 3-hydroxy-3-methylbutyl, 2-hydroxyethyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

For each of the embodiments described in the paragraph immediately following Formulas Ip¹ and Ip³, R¹ is preferably methyl or ethyl; R² is phenyl optionally substituted with 1, 2 or 3 substituents selected from halo, cyano, CONH_2 , (C₁-C₄)alkyl, (C₁-C₄)haloalkyl and SO_2Me ; and R³ is $\text{H}_2\text{NC}(=\text{O})\text{CMe}_2\text{CH}_2$, 3-hydroxy-3-methylbutyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

For each of the embodiments described in the paragraph immediately following Formulas Ip¹ and Ip³, R¹ is preferably methyl or ethyl; and R³ is 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

For each of the embodiments described in the paragraph immediately following Formulas Ip¹ and Ip³, R¹ is preferably methyl or ethyl; R² is phenyl or fluorophenyl; and R³ is 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl.

For each of the embodiment described in the paragraph immediately following Formulas Ip¹ and Ip³, R¹ is preferably methyl or ethyl; R² is phenyl or fluorophenyl; R³ is 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl; the substituent G^{2a} is selected from (C₁-C₄)alkyl, (C₃-C₄)cycloalkyl, (C₃-C₄)cycloalkyl(C₁-C₂)alkyl, and (C₁-C₂)haloalkyl; and G^{2b} is optionally selected from hydrogen, methyl or ethyl.

For each of the embodiment described in the paragraph immediately following Formulas Ip¹ and Ip³, R¹ is preferably methyl or ethyl; R² is phenyl or fluorophenyl; R³ is 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl; the substituent G^{2a} is selected from haloalkyl, (C₁-C₄)alkyl, (C₃-C₄)cycloalkyl, (C₃-C₄)cycloalkyl(C₁-C₂)alkyl, and (C₁-C₂)haloalkyl; and G^{2b} is optionally selected from hydrogen, methyl or ethyl.

For each of the embodiment described in the paragraph immediately following Formulas Ip¹ and Ip³, R¹ is preferably methyl or ethyl; R² is phenyl or fluorophenyl; R³ is 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl; the substituent G^{2a} is selected from difluoromethyl, ethyl substituted with one to three fluorine (preferably, 2-fluoroethyl or 2,2,2-fluoroethyl), (C₁-C₄) alkyl, (C₃-C₄) cycloalkyl, (C₃-C₄) cycloalkyl(C₁-C₂) alkyl, and (C₁-C₂) haloalkyl; and G^{2b} is optionally selected from hydrogen, methyl or ethyl.

Another embodiment of the invention (referred to herein as the "Second Alternate Embodiment") is a compound represented by Structural Formulas Ip¹ and Ip³, wherein: n is 0 or 1, preferably 0; each G¹ is independently (C₁-C₄) alkyl, (C₁-C₄) alkoxy, (C₁-C₄) haloalkyl, (C₁-C₄) haloalkoxy, halogen, cyano or nitro; G^{2a} is hydroxy(C₁-C₆) alkyl, (C₁-C₆) alkylcarbonylamino(C₁-C₆) alkyl, (C₁-C₆) alkylsulfonylamino(C₁-C₆) alkyl, (C₁-C₆) alkoxy(C₁-C₆) alkyl, amino(C₁-C₆) alkyl, (C₁-C₆) alkylamino(C₁-C₆) alkyl, di(C₁-C₆) alkylamino(C₁-C₆) alkyl, cyano(C₁-C₆) alkyl, aminocarbonyl(C₁-C₆) alkyl, (C₁-C₆) alkylaminocarbonyl(C₁-C₆) alkyl, di(C₁-C₆) alkylaminocarbonyl(C₁-C₆) alkyl, (C₃-C₆) cycloalkylaminocarbonyl(C₁-C₆) alkyl, {(C₃-C₆) cycloalkyl}{(C₁-C₆) alkyl}aminocarbonyl(C₁-C₆) alkyl or di(C₃-C₆) cycloalkylaminocarbonyl(C₁-C₆) alkyl; G^{2b} is hydrogen, fluorine, chlorine, cyano, hydroxy, amino, (C₁-C₄) alkyl, (C₃-C₄) cycloalkyl, (C₃-C₄) cycloalkyl(C₁-C₂) alkyl, halo(C₁-C₄) alkyl, (C₁-C₄) alkoxy, (C₁-C₄) haloalkoxy, CONH₂, (C₁-C₄) alkylaminocarbonyl, di(C₁-C₄) alkylaminocarbonyl or (C₁-C₄) alkylcarbonylamino; R¹ is methyl or ethyl; R² is phenyl, thienyl, pyridyl or isopropyl each optionally substituted with up to three groups independently selected from halo, methyl, methylthio or (4-morpholino)methyl; and R³ is methyl, ethyl, propyl, butyl, vinyl, allyl or ethoxyethyl each optionally substituted with up to two groups independently selected from methyl, HO-, MeO-, H₂N-, MeC(=O)NH-, MeS(=O)₂NH-, H₂NC(=O)-, MeNHC(=O)-, HO₂C-, (HO)₂P(=O)O-, H₂NS(=O)₂O-, H₂NS(=O)₂NH-, MeNHC(=O)NH-, MeNHC(=O)O-, oxo, cyano, HO₂C-, HOCH₂CH₂NH-, 4-morpholino, HOCH₂C(=O)NH-, H₂NCH₂C(=O)NH-, EtNHC(=O)NH-, MeOC(=O)NH-, MeNHC(=NC≡N)NH-, Me-, MeS-, MeSO₂-, MeSO₂N(Me)-, MeS(=O)₂NHC(=O)-, imidazolylamino-, imidazolyl, tetrazolyl, H₂NCONH-, H₂NCO₂-, HOCH₂CH₂O-, MeNH-, Me₂N- and MeCONMe.

Alternatively for Structural Formulas Ip¹ and Ip³, R² is phenyl optionally substituted with 1, 2 or 3 substituents independently selected from halo, cyano, CONH₂, (C₁-C₄) alkyl, (C₁-C₄) haloalkyl and SO₂Me; and R³ is is MeSO₂NHCH₂CH₂CH₂, H₂NC(=O)CH₂CH₂, H₂NC(=O)CMe₂CH₂, 3-hydroxypropyl, 3-hydroxy-3-methylbutyl, 2-

hydroxyethyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl; and the remainder of the variables are as described above for the Second Alternate Embodiment.

Alternatively for Structural Formulas Ip¹ and Ip³, R³ is H₂NC(=O)CMe₂CH₂, 3-hydroxy-3-methylbutyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl; and the remainder of the variables are as described above for the Second Alternate Embodiment.

Alternatively for Structural Formulas Ip¹ and Ip³, R² is phenyl optionally substituted with 1, 2 or 3 substituents independently selected from halo, cyano, CONH₂, (C₁-C₄)alkyl, (C₁-C₄)haloalkyl and SO₂Me; and R³ is H₂NC(=O)CMe₂CH₂, 3-hydroxy-3-methylbutyl, 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl; and the remainder of the variables are as described in the Second Alternate Embodiment.

Alternatively for Structural Formulas Ip¹ and Ip³, R³ is 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl; and the remainder of the variables are as described in the Second Alternate Embodiment.

Alternatively for Structural Formulas Ip¹ and Ip³, R² is phenyl or fluorophenyl; and R³ is 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl; and the remainder of the variables are as described in the Second Alternate Embodiment.

Alternatively for Structural Formulas Ip¹ and Ip³, R² is phenyl or fluorophenyl; R³ is 2-hydroxy-2-methylpropyl or 2-cyano-2-methylpropyl; one or two substitutable ring carbon atoms in the oxodihydropyridyl rings are optionally substituted with fluorine, methyl or ethyl; and the remainder of the variables are as described in the Second Alternate Embodiment.

For the embodiment described in the previous seven paragraphs, n is 0 and G^{2b} is preferably -H.

Compounds of the invention are also disclosed in INHIBITORS OF 11 β -HYDROXYSTEROID DEHYDOGENASE I, U.S. Provisional Application No. 61/61/135,933, filed July 25, 2008 (Attorney Docket No. 4370.1000-000); Cyclic Inhibitors Of 11 β -Hydroxysteroid Dehydrogenase 1, U.S. Provisional Application No. 61/135,933, filed May 1, 2008; Cyclic Inhibitors Of 11 β -Hydroxysteroid Dehydrogenase 1, U.S. Provisional Application No. 61/137,148, filed July 25, 2008; and Cyclic Inhibitors Of 11 β -Hydroxysteroid Dehydrogenase 1, International Application No. PCT/US2008/009017, filed July 25, 2008; the entire teachings of these applications are incorporated herein by reference in their entirety.

DEFINITIONS

The term "alkyl" means a straight or branched hydrocarbon radical having 1-10 carbon atoms and includes, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, n-nonyl, n-decyl and the like.

The term "cycloalkyl" means a monocyclic, bicyclic or tricyclic, saturated hydrocarbon ring having 3-10 carbon atoms and includes, for example, cyclopropyl (c-Pr), 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 "aryl" means an aromatic radical which is a phenyl group, a naphthyl group, an indanyl group or a tetrahydronaphthalene group. An aryl group is optionally substituted with 1-4 substituents. Exemplary substituents include alkyl, alkoxy, alkylthio, alkylsulfonyl, halogen, trifluoromethyl, dialkylamino, nitro, cyano, CO₂H, CONH₂, N-monoalkyl-substituted amido and N,N-dialkyl-substituted amido.

The term "heteroaryl" means a 5- and 6-membered heteroaromatic radical which may optionally be fused to a saturated or unsaturated ring containing 0-4 heteroatoms selected from N, O, and S and includes, for example, a heteroaromatic radical which is 2- or 3-thienyl, 2- or 3-furanyl, 2- or 3-pyrrolyl, 2-, 3-, or 4-pyridyl, 2-pyrazinyl, 2-, 4-, or 5-pyrimidinyl, 3- or 4-pyridazinyl, 1H-indol-6-yl, 1H-indol-5-yl, 1H-benzimidazol-6-yl, 1H-benzimidazol-5-yl, 2-, 4-, 5-, 6-, 7- or 8-quinazolinyl, 2-, 3-, 5-, 6-, 7- or 8-quinoxaliny, 2-, 3-, 4-, 5-, 6-, 7- or 8-quinolinyl, 1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinolinyl, 2-, 4-, or 5-thiazolyl, 2-, 3-, 4-, or 5-pyrazolyl, 2-, 3-, 4-, or 5-imidazolyl. A heteroaryl is optionally substituted. Exemplary substituents include alkyl, alkoxy, alkylthio, alkylsulfonyl, halogen, trifluoromethyl, dialkylamino, nitro, cyano, CO₂H, CONH₂, N-monoalkyl-substituted amido and N,N-dialkyl-substituted amido, or by oxo to form an N-oxide.

The term "heterocyclyl" means a 4-, 5-, 6- and 7-membered saturated or partially unsaturated heterocyclic ring containing 1 to 4 heteroatoms independently selected from N, O, and S. Exemplary heterocyclyls include pyrrolidine, pyrrolidin-2-one, 1-methylpyrrolidin-2-one, piperidine, piperidin-2-one, dihydropyridine, tetrahydropyridine, piperazine, 1-(2,2,2-trifluoroethyl)piperazine, 1,2-dihydro-2-oxopyridine, 1,4-dihydro-4-oxopyridine, piperazin-2-one, 3,4,5,6-tetrahydro-4-oxopyrimidine, 3,4-dihydro-4-oxopyrimidine, 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 isothiazolidine 1,1-dioxide, 6-oxo-1,6-dihydropyridazin-3-yl, 6-oxo-1,6-dihydropyridazin-4-yl, 5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl and 5-oxo-4,5-dihydro-1H-imidazol-2-yl. A heterocyclcyl can be optionally substituted with 1-4 substituents. Exemplary substituents include alkyl, haloalkyl, halogen and oxo.

The term "spirocycloalkyl" means a cycloalkyl group which shares one ring carbon with another alkyl or cycloalkyl group.

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, 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.

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, 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 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. The symbol "*" in a structural formula represents the presence of a chiral carbon center. "R" and "S" represent the configuration of substituents around one or more chiral carbon atoms. Thus, "R*" and "S*" denote the relative configurations of substituents around one or more chiral carbon atoms.

"Racemate" or "racemic mixture" means a compound of equimolar quantities of 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 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 relative to the core molecule.

The compounds of the invention may be prepared as individual isomers by either isomer-specific synthesis or resolved from an isomeric mixture. Conventional 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 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 structure, the named or depicted stereoisomer is at least 60%, 70%, 80%, 90%, 99% or 99.9% by weight 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 weight optically pure. Percent optical purity by weight is the ratio of the weight of the enantiomer over the weight of the enantiomer plus the weight of its optical isomer.

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 one enantiomer of compound free from the corresponding optical isomer, a racemic mixture of the compound and mixtures enriched in one enantiomer relative to its corresponding optical isomer.

When a disclosed compound is named or depicted by structure without indicating the stereochemistry and has at least two chiral centers, it is to be understood that the

name or structure encompasses a diastereomer free of other diastereomers, a pair of diastereomers free from other diastereomeric pairs, mixtures of diastereomers, mixtures of diastereomeric pairs, mixtures of diastereomers in which one diastereomer is enriched relative to the other diastereomer(s) and mixtures of diastereomeric pairs in which one diastereomeric pair is enriched relative to the other diastereomeric pair(s).

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

The following abbreviations have the indicated meanings:

Abbreviation	Meaning
A%	Area percentage
Boc	<i>tert</i> -butoxy carbonyl or <i>t</i> -butoxy carbonyl
(Boc) ₂ O	di- <i>tert</i> -butyl dicarbonate
Cbz	Benzyloxycarbonyl
CbzCl	Benzyl chloroformate
c-Pr	cyclopropyl

DAST	diethylaminosulfur trifluoride
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	N,N'-dicyclohexylcarbodiimide
DCU	N,N'-dicyclohexylurea
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminum hydride
DIEA	N,N-diisopropylethylamine
DMAP	4-(dimethylamino)pyridine
DMF	N,N-dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
2,4-DNP	2,4-dinitrophenylhydrazine
dppf	1,1'-Bis(diphenylphosphino)ferrocene
DPTBS	Diphenyl-t-butylsilyl
dr	diastereomer ratio
EDC.HCl, EDCI	1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride
Equiv	equivalents
EtOAc	Ethyl acetate
Fmoc	1-[[[(9H-fluoren-9-ylmethoxy)carbonyl]oxy]-
Fmoc-OSu	1-[[[(9H-fluoren-9-ylmethoxy)carbonyl]oxy]-2,5-pyrrolidinedione
h, hr	hour(s)
HOBt	1-hydroxybenzotriazole
HATU	2-(7-Aza-1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HBTU	2-(1H-Benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
KHMDS	potassium hexamethyldisilazane

LAH or LiAlH ₄	lithium aluminum hydride
LC-MS	liquid chromatography-mass spectroscopy
LHMDS	lithium hexamethyldisilazane
m-CPBA	meta-chloroperoxybenzoic acid
Me	methyl
MsCl	methanesulfonyl chloride
Min	minute
MS	mass spectrum
NaH	sodium hydride
NaHCO ₃	sodium bicarbonate
NaN ₃	sodium azide
NaOH	sodium hydroxide
Na ₂ SO ₄	sodium sulfate
NMM	N-methylmorpholine
NMP	N-methylpyrrolidinone
Pd ₂ (dba) ₃	tris(dibenzylideneacetone)dipalladium(0)
PE	petroleum ether
Quant	quantitative yield
rt	room temperature
Satd	saturated
SOCl ₂	thionyl chloride
SFC	supercritical fluid chromatography
SPA	scintillation proximity assay
SPE	solid phase extraction
TBAF	tetrabutylammonium fluoride
TBS	t-butyldimethylsilyl

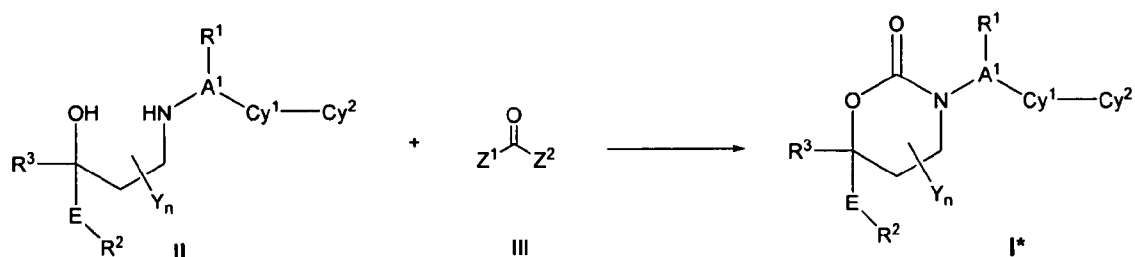
TBDPS	t-butyldiphenylsilyl
TBSCI	t-butyldimethylsilyl chloride
TBDPSCI	t-butyldiphenylsilyl chloride
TEA	triethylamine or Et ₃ N
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy free radical
Teoc	1-[2-(trimethylsilyl)ethoxycarbonyloxy]-
Teoc-OSu	1-[2-(trimethylsilyl)ethoxycarbonyloxy]pyrrolidin-2,5-dione
T _{ext}	External temperature
T _{int}	Internal temperature
TFA	trifluoroacetic acid
Tlc, TLC	thin layer chromatography
TMS	trimethylsilyl
TMSCI	chlorotrimethylsilane or trimethylsilyl chloride
t _R	retention time
TsOH	p-toluenesulfonic acid

GENERAL DESCRIPTION OF SYNTHETIC METHODS

Compounds of Formula I* can be prepared by several processes. In the discussion below, A¹, Cy¹, E, R¹, R², R³, Y and n have the meanings indicated above unless otherwise noted. Cy² is an optionally substituted 2-oxo-1,2-dihydropyridyl group. In cases where the synthetic intermediates and final products of Formula I* described below contain potentially reactive functional groups, for example amino, hydroxyl, thiol and carboxylic acid groups, that may interfere with the desired reaction, it may be advantageous to employ protected forms of the intermediate. Methods for the selection, introduction and subsequent removal of protecting groups are well known to those skilled in the art. (T.W. Greene and P. G. M. Wuts "Protective Groups in Organic Synthesis" John Wiley & Sons, Inc., New York 1999). Such protecting group manipulations are assumed in the discussion below and not described explicitly. Generally, reagents in the reaction schemes are used in equimolar amounts; however, in certain cases it may be desirable to use an excess of one reagent to drive a reaction to completion. This is especially the case when the excess reagent can be readily removed by evaporation or

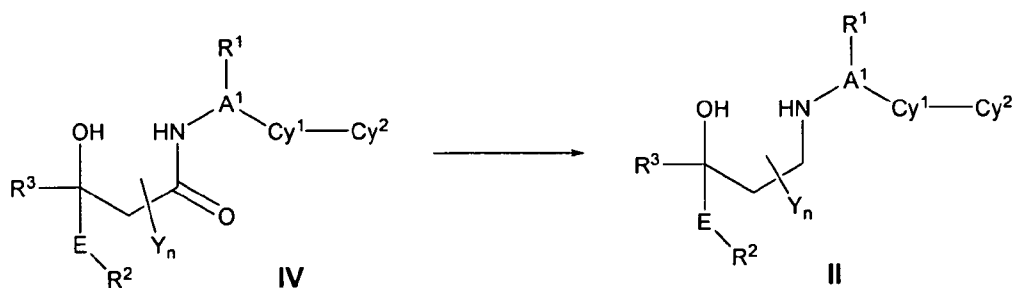
extraction. Bases employed to neutralize HCl in reaction mixtures are generally used in slight to substantial excess (1.05 – 5 equivalents).

In a first process a compound of Formula I*, can be prepared by reaction of an aminoalcohol intermediate of Formula II with a reagent of Formula III, wherein Z¹ and Z² are leaving groups such as chloride, 1-imidazolyl or aryloxy in an inert solvent such as THF, CH₂Cl₂, toluene or MeCN, usually in the presence of an organic or inorganic base such as triethylamine or NaHCO₃ respectively, at -10 °C to 120 °C:

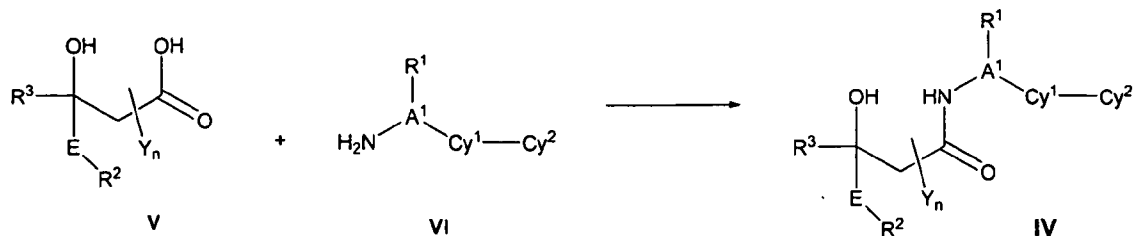


Certain instances of reagent III are especially convenient because they are commercially available. For example when Z¹ and Z² are both chloride, III is phosgene. When Z¹ and Z² are both 1-imidazolyl, III is carbonyl diimidazole. When Z¹ is chloride and Z² is p-nitrophenoxide, III is p-nitrophenyl chloroformate. When Z¹ and Z² are both OCCl₃, III is triphosgene and as little as one third of molar equivalent can be used.

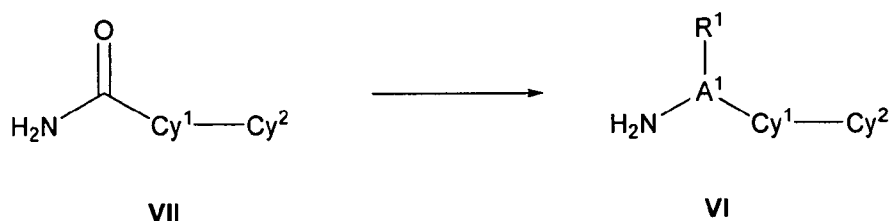
Aminoalcohol intermediates of Formula II can be prepared by reduction of amides of Formula IV using a hydride reagent such as BH₃.THF solution, BH₃.Me₂S or LiAlH₄ in an inert solvent ethereal such as THF or DME at 20 °C to 100 °C for between 1 h and 48 h:



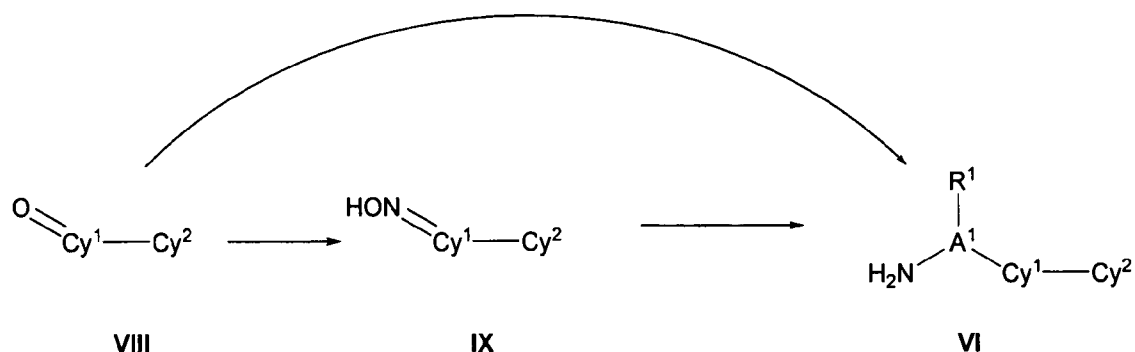
Intermediates of Formula IV can be prepared by coupling of a β-hydroxyacid of Formula V with an amine of Formula VI using standard peptide coupling reagents such as EDC in the presence of HOBt and N,N-diisopropylethylamine in an inert solvent such as CH₂Cl₂ at 0 – 30 °C for between 1 h and 24 h:



Amine intermediates of Formula VI, wherein $\text{A}^1 = \text{CH}_2$ and R^1 is absent, can be prepared by reduction of amides of Formula VII using a hydride reagent such as BH_3 .THF solution, $\text{BH}_3\cdot\text{Me}_2\text{S}$ or LiAlH_4 in an inert solvent ethereal such as THF or DME at 20 °C to 100 °C for between 1 h and 48 h:

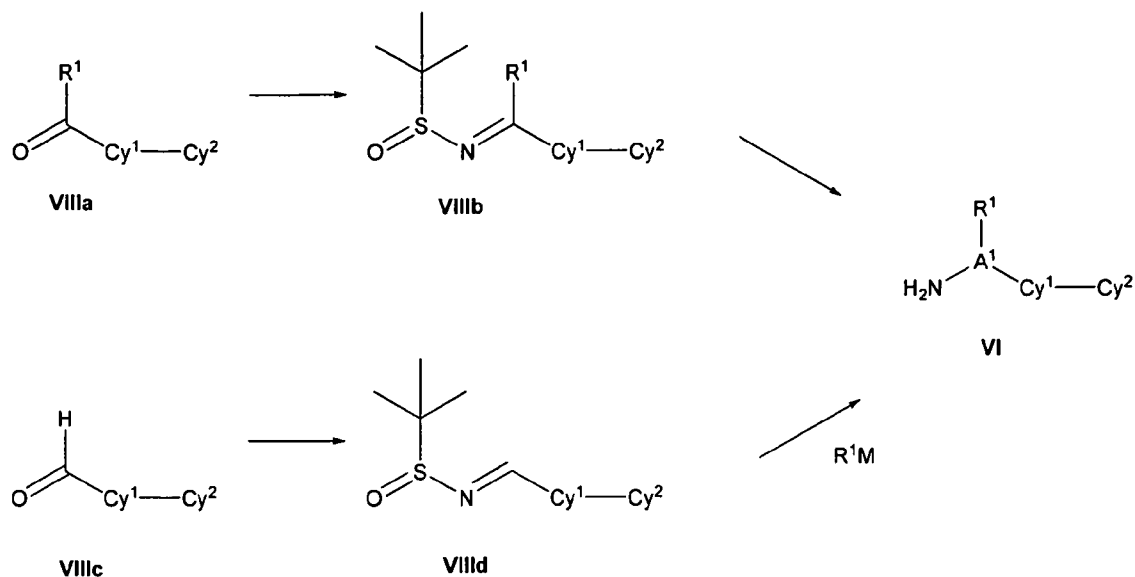


Amine intermediates of Formula VI, wherein A^1 is a bond, R^1 is absent and Cy^1 is not an aromatic or heteroaromatic ring, can be prepared from ketones of formula VIII via oximes of Formula IX or by reductive amination of a ketone of Formula VIII with ammonia:



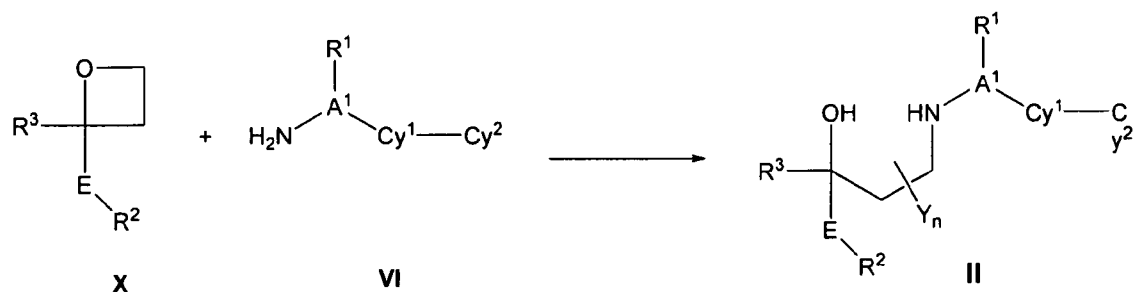
Methods for the conversion of ketones to oximes are described in Smith, M. B. and March, J. "March's Advanced Organic Chemistry" pp 1194-1195, 5th Edition, Wiley, New York, NY, 2001. Methods for the reduction of oximes to primary amines are described in Smith, M. B. and March, J. "March's Advanced Organic Chemistry" p 1555, 5th Edition, Wiley, New York, NY, 2001. Methods for the reductive amination of ketones are described in Baxter, E. W. and Reitz, A. B. "Organic Reactions" Volume 59, Ed. Overman, L. E., Wiley Interscience, 2002.

Similarly amine intermediates of Formula VI, wherein A^1 is CH and R^1 is methyl or ethyl, can be prepared by reduction *t*-butylsulfinylimines of Formula VIIIb which can be prepared from ketones of Formula VIIIa and *t*-butylsulfinamide or by addition of organometallic reagents of Formula R^1M , wherein R^1 is Me or Et and M is Li, MgCl, MgBr or MgI, to *t*-butylsulfinylimines of Formula VIIIc which can be prepared from aldehydes of Formula VIIIc.

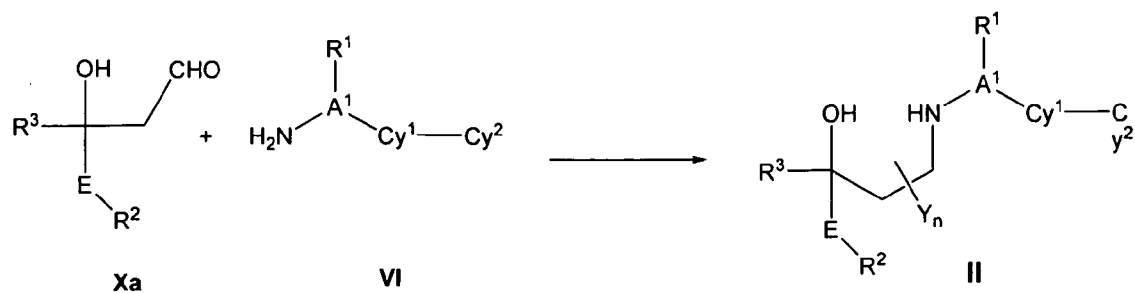


High stereoselectivity is often achieved in such reactions using chiral *t*-butylsulfinylamines.

Intermediates of Formula II, wherein $n = 0$, can be prepared by reaction of oxetanes of Formula X with amines of Formula VI as described in Smith, M. B. and March, J. "March's Advanced Organic Chemistry" p 505, 5th Edition, Wiley, New York, NY, 2001:

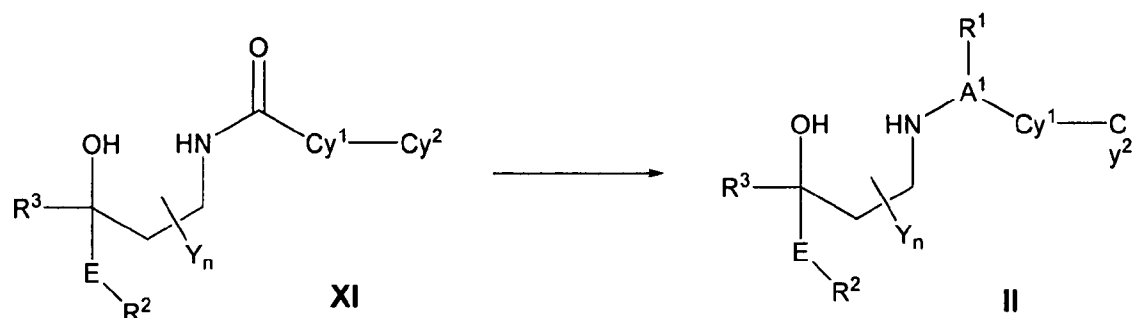


Intermediates of Formula II can also be prepared by reductive amination of β -hydroxyaldehydes of Formula Xa with amines of Formula VI. Methods for the reductive amination of aldehydes are described in Baxter, E. W. and Reitz, A. B. "Organic Reactions" Volume 59, Ed. Overman, L. E., Wiley Interscience, 2002.

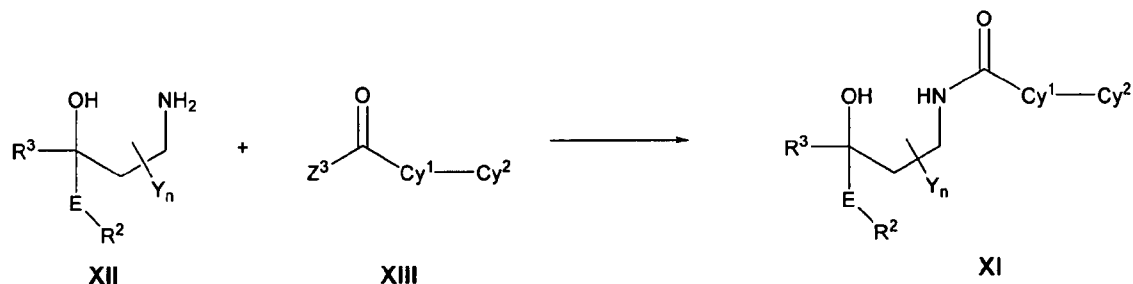


Aldehydes of Formula Xa can be prepared from homoallylic alcohols of Formula XXI by treatment with OsO_4 and NaIO_4 .

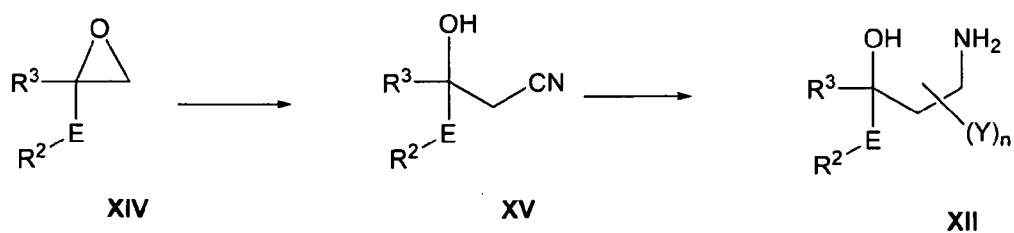
- Intermediates of Formula II, wherein $\text{A}^1 = \text{CH}_2$ and R^1 is absent, can be prepared by reduction of amide intermediates of formula XI using a hydride reagent such as BH_3 .THF solution, $\text{BH}_3\cdot\text{Me}_2\text{S}$ or LiAlH_4 in an inert solvent ethereal such as THF or DME at 20 °C to 100 °C for between 1 h and 48 h:



- Amide intermediates of Formula XI can be prepared by reaction of an amino-alcohol intermediate of Formula XII with activated carboxylic acid of Formula XIII wherein $\text{Z}^3 = \text{chloride}$ or an activated ester, such as an N-hydroxysuccinimide ester:



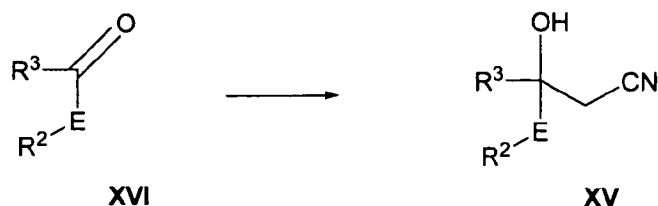
- Amino-alcohol intermediates of Formula XII, wherein $n = 0$, can be prepared by reaction of an epoxide of Formula XIV with cyanide ion followed by reduction of the resulting hydroxynitrile of Formula XV with hydrogen gas in the presence of a catalyst or with a hydride source such as LiAlH_4 :



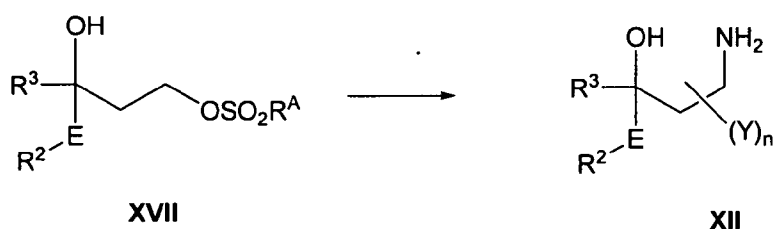
- Epoxide compounds of formula XIV can, in turn, be prepared in a number of ways including, as described in Aube, J. "Epoxidation and Related Processes" Chapter 3.2 in Volume 1 of

"Comprehensive Organic Synthesis" Edited by B. M. Trost, I. Fleming and Stuart L. Schreiber, Pergamon Press, New York, 1992.

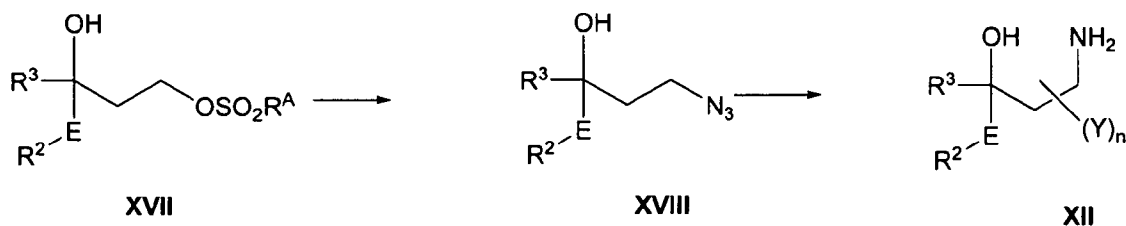
Hydroxynitrile intermediates of Formula XV can be prepared by treatment of ketones of Formula XVI with acetonitrile anion, formed by treatment of acetonitrile with *n*-BuLi or LDA, in an inert, anhydrous solvent such as THF at low temperature:



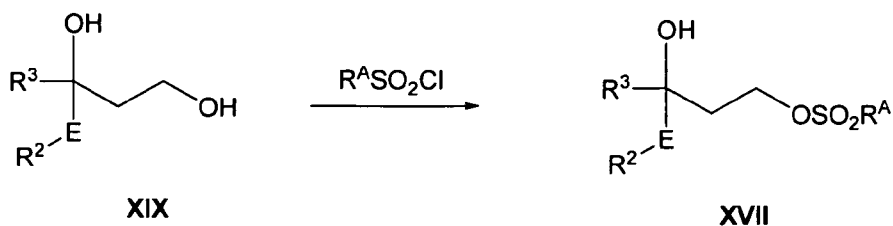
Amino-alcohol intermediates of Formula XII, wherein *n* is 0, can be prepared by treatment of sulfonate intermediates of Formula XVII, wherein *R*^A is for example methyl, trifluoromethyl or *p*-methylphenyl, with ammonia:



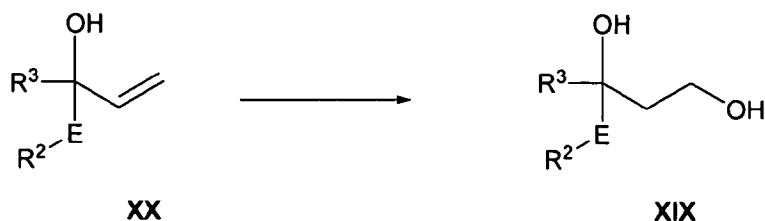
Amino-alcohol intermediates of Formula XII can be prepared by treatment of sulfonate intermediates of Formula XVII with sodium azide to give an azide intermediate of Formula XVIII, followed by catalytic hydrogenation or by Staudinger reduction with PPh₃ in wet THF:



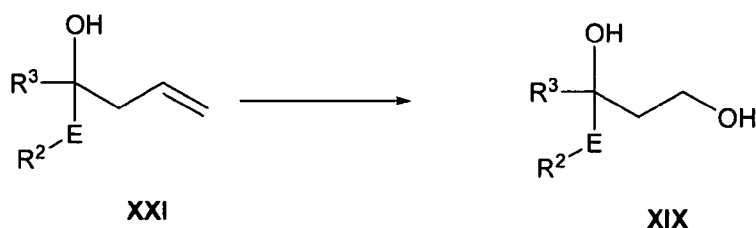
Sulfonate intermediates of Formula XVII can be prepared from diol intermediates of Formula XIX with a sulfonyl chloride *R*^ASO₂Cl:



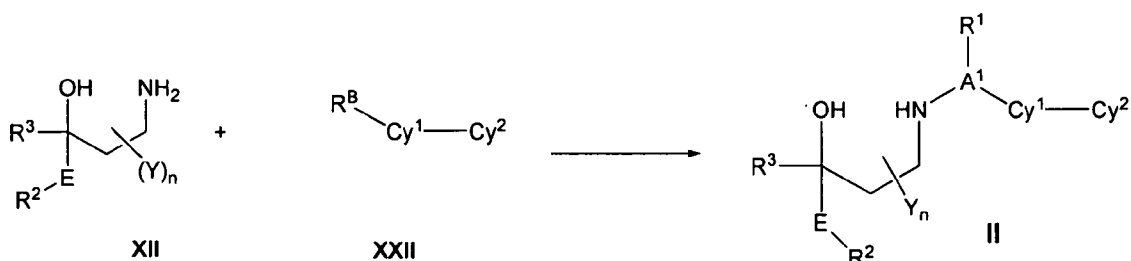
Diol intermediates of Formula XIX can be prepared by hydroboration of allyl alcohols of Formula XX:



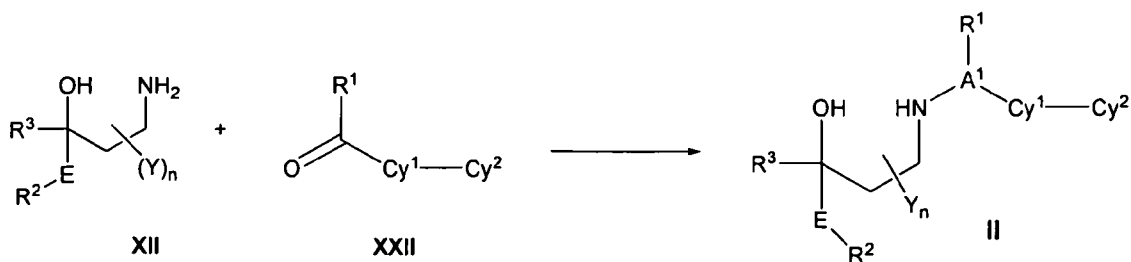
Diol intermediates of Formula XIX can be prepared by ozonolysis and reduction of homoallyl alcohols of Formula XXI:



Aminoalcohol intermediates of Formula II, wherein A^1 is a bond, R^1 is absent, and Cy^1 is a heteroaryl group or an aryl group bearing at least one strongly electron withdrawing group such as CF_3 , can be prepared by reaction of an aminoalcohol intermediate of Formula XII with a compound of Formula XXII, wherein Cy^1 is a heteroaryl group or an aryl group bearing at least one strongly electron withdrawing group such as CF_3 and R^B is a leaving group such a fluoro, chloro, bromo or iodo:

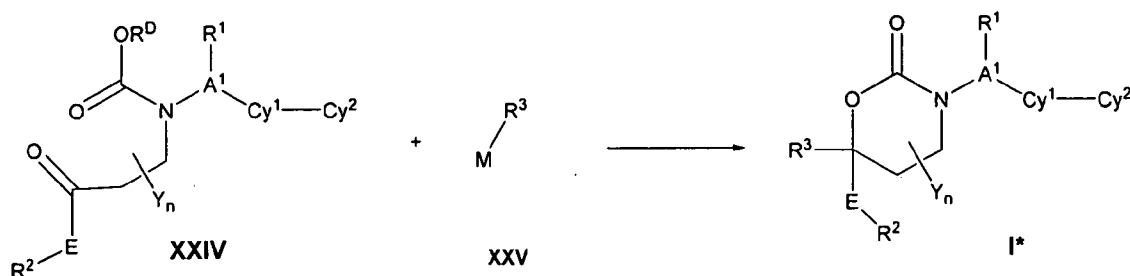


Aminoalcohol intermediates of Formula II, wherein A^1 is (C_1) alkylene can be prepared by reaction of an aminoalcohol of Formula XII with an aldehyde or methyl ketone of Formula XXII in the presence of a reducing agent such as $NaCNBH_3$ or $Na(OAc)_3BH$:



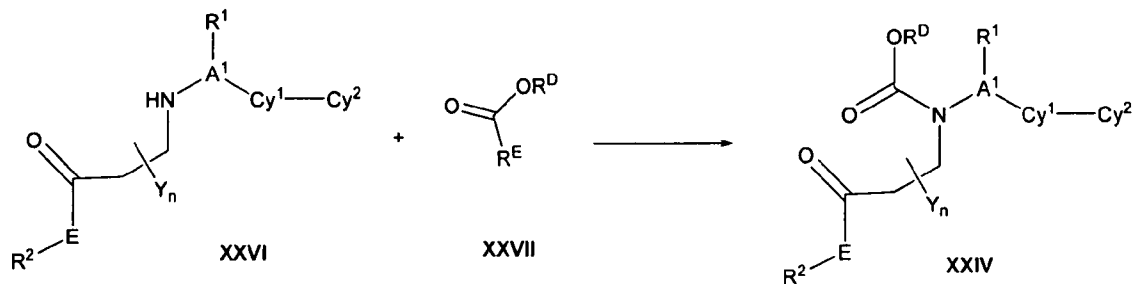
Methods for the reductive amination of aldehydes and ketones are described in Baxter, E. W. and Reitz, A. B. "Organic Reactions" Volume 59, Ed. Overman, L. E., Wiley Interscience, 2002.

In a second process a compound of Formula I* can be prepared by reaction of a ketocarbamate of Formula XXIV, wherein R^D is alkyl or arylalkyl group such as methyl, t-butyl or benzyl, with an organometallic reagent of Formula XXV wherein M includes, but is not limited to, MgCl, MgBr, MgI or Li:

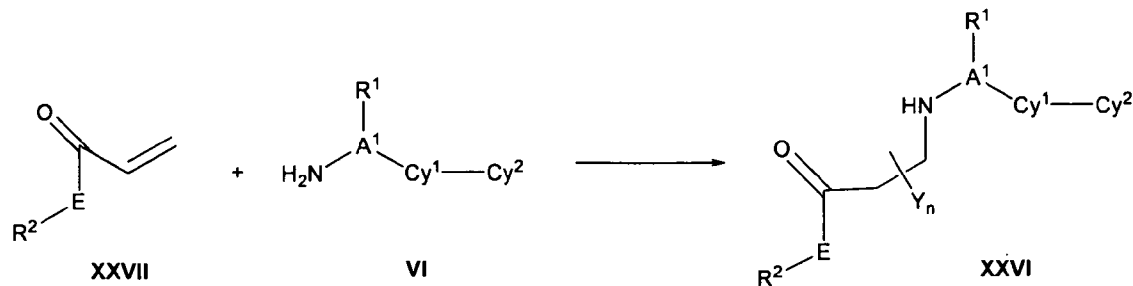


In specific examples, organometallic reagent XXV is allylmagnesium bromide, allylzinc(II) bromide, (2-methylallyl)magnesium chloride or (2-methoxy-2-oxoethyl)zinc(II) bromide. In certain cases when M is MgCl, MgBr or MgI, it is advantageous to add CeCl₃ to the reaction mixture.

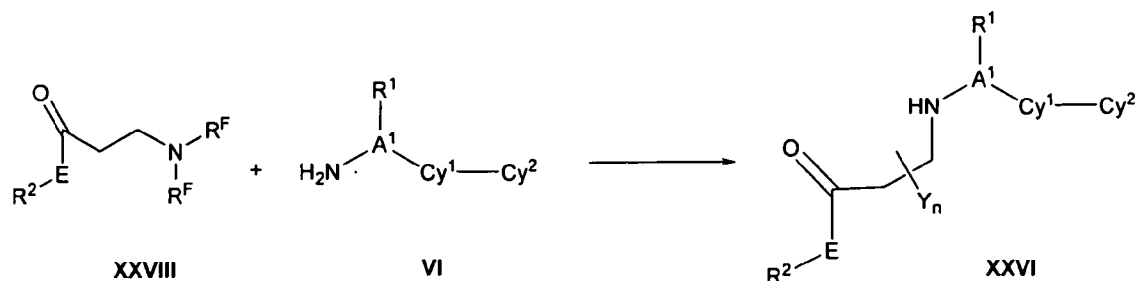
Ketocarbamates of Formula XXIV can be prepared by reaction of aminoketones of Formula XXVI with intermediates of Formula XXVII wherein R^E is a leaving group such as chloride, succinyloxy, imidazolyl or t-butoxycarboxycarbonyl:



Aminoketones of Formula XXVI, wherein n = 0, can be prepared by reaction of α,β-unsaturated ketones of Formula XXVIII with amines of Formula VI:

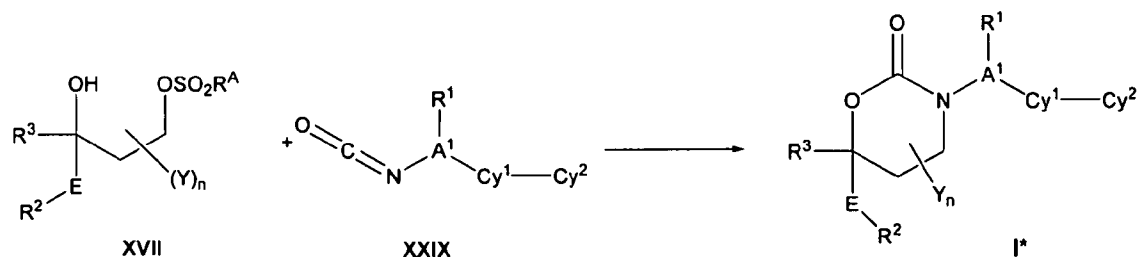


Aminoketones of Formula XXVI, wherein n = 0, can be prepared by reaction of β-dialkylaminoketones of Formula XXVIII, wherein R^F is lower alkyl especially methyl, with amines of Formula VI:



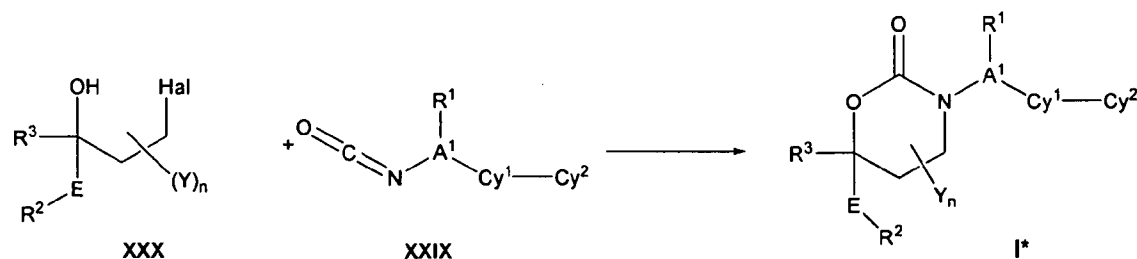
β -Dialkylaminoketones of Formula XXVIII are in turn derived from α , β -unsaturated ketones of Formula XXVII with dialkylamines of Formula $R^F NHR^F$.

- 5 In a third process a compound of Formula I* can be prepared by reaction of a compound of Formula XVII with an isocyanate of Formula XXIX in the presence of a base:



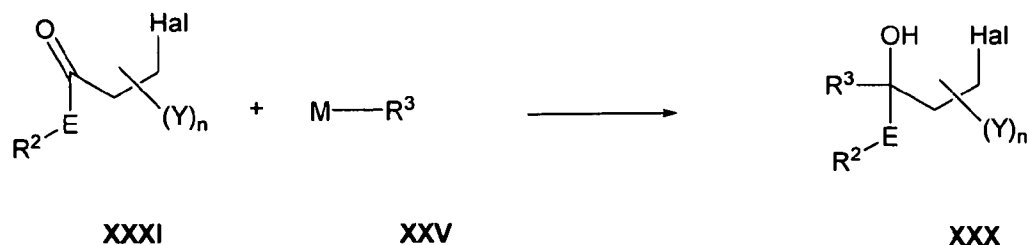
- 10 Isocyanates of Formula XXIX can be prepared from amines of Formula VI by treatment with phosgene, diphosgene or triphosgene. This third process is described in greater detail in U.S. Provisional Application Serial No. 61/137,013, filed July 25, 2008 entitled SYNTHESIS OF INHIBITORS OF 11β -HYDROXYSTERIOD DEHYDROGENASE TYPE 1 (Attorney Docket No. 4370.1001-000), the entire teachings of which are incorporated herein by reference.

In a fourth process a compound of Formula I* can be prepared by reaction of a halo compound of Formula, wherein Hal is chlorine or bromine, with an isocyanate of Formula XXIX in the presence of a base:

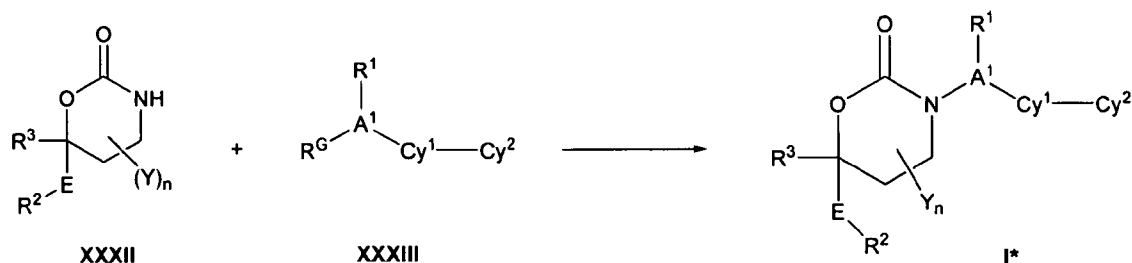


15 Halo compounds of Formula XXX can be prepared by reaction of β -haloketones of Formula XXXI with organometallic reagents of Formula XXV wherein M is a metal containing radical including $MgCl$, $MgBr$, MgI or Li . The reaction is optionally carried out in the presence of anhydrous cerium trichloride:

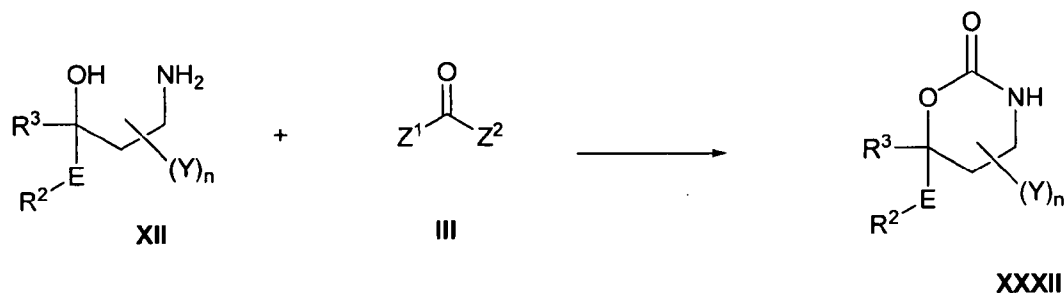
- 44 -



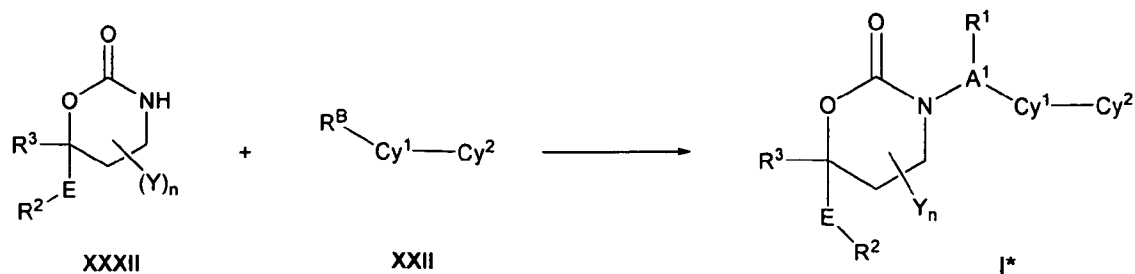
In a fifth process a compound of Formula I*, wherein A¹ is CH₂ or CH₂CH₂ and R¹ is absent, can be prepared by reaction of a compound of Formula XXXII, with a compound of Formula XXXIII, wherein A¹ is CH₂ or CH₂CH₂ and R^G is a leaving group such as Br, I, OSO₂Me, OSO₂CF₃ or OSO₂Ph, in the presence of a base such as NaH or K₂CO₃:



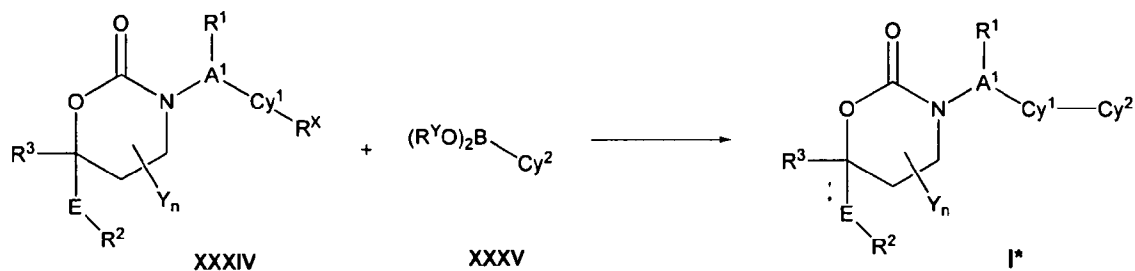
Compounds of Formula XXXII can be prepared by treatment of compounds of Formula XII with various reagents of Formula III, wherein Z¹ and Z² are leaving groups such as chloride, 1-imidazolyl or aryloxy in an inert solvent such as THF, CH₂Cl₂, toluene or MeCN, usually in the presence of an organic or inorganic base such as triethylamine or NaHCO₃ respectively, at -10 °C to 120 °C:



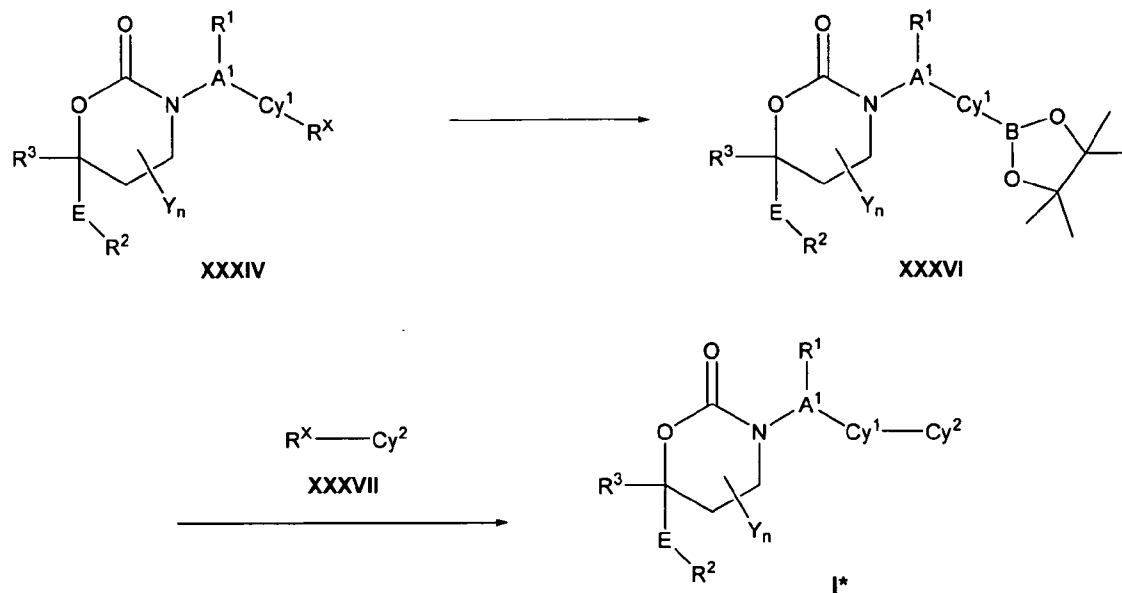
In a sixth process a compound of Formula I*, wherein A¹ is a bond and R¹ is absent, can be prepared by reaction of a compound of Formula XXXII, with a compound of Formula XXII, wherein R^B is a leaving group such as chloro, bromo, iodo or OSO₂CF₃, in the presence of a base such as K₂CO₃ and a copper or palladium catalyst in an inert solvent such as dioxane, DMF or NMP at elevated temperature:



In a seventh process a compound of Formula I* can be prepared by Suzuki coupling of a compound of Formula XXXIV, wherein Cy^1 is aryl or heteroaryl and R^X is bromo, iodo, or trifluoromethanesulfonyloxy, with a boronic acid (R^Y is hydrogen) or a boronate ester of Formula XXXV (R^Y is (C_1-C_6) alkyl and the two groups R^Y taken together form a (C_1-C_{12}) alkylene group).



In an eighth process a compound of Formula XXXIV, wherein Cy^1 is aryl or heteroaryl and R^X is bromo, iodo, or trifluoromethanesulfonyloxy, can be reacted with bis(pinacolato)diboron in the presence of a palladium catalyst to give a boronate ester of Formula XXXVI which can be further reacted with a heterocyclic compound of Formula XXXVII, wherein R^X is bromo, iodo, or trifluoromethanesulfonyloxy, again in the presence of a palladium catalyst, to give a compound of Formula I*.



In a ninth process a compound of Formula I* can be prepared from another compound of Formula I*. For example:

- 5 (1) a compound of Formula I*, wherein R¹ or R³ is ω-hydroxy(C₂-C₆)alkyl, can be oxidized to a compound of Formula I*, wherein R¹ or R³ is ω-carboxy(C₁-C₅)alkyl, using Jones reagent.
- (2) a compound of Formula I*, wherein R¹ or R³ is ω-carboxy(C₁-C₆)alkyl, can be coupled with ammonia or a (C₁-C₆)alkylamine using a standard peptide coupling reagent such as EDC to afford a compound of Formula I*, wherein R¹ or R³ is ω-H₂NC(=O)(C₁-C₆)alkyl or ω-((C₁-C₆)alkyl)NHC(=O)(C₁-C₆)alkyl.
- 10 (3) a compound of Formula I*, wherein R¹ or R³ is ω-hydroxy(C₁-C₆)alkyl, can be converted to its methanesulfonate or trifluoromethanesulfonate, treated with sodium azide and reduced to give a compound of Formula I*, wherein R¹ or R³ is ω-amino(C₁-C₆)alkyl.
- (4) a compound of Formula I*, wherein R¹ or R³ is amino(C₁-C₆)alkyl, can be reacted with acetic anhydride or acetyl chloride to give a compound of Formula I*, wherein R¹ or R³ is {acetylamino}(C₁-C₆)alkyl.
- 15 (5) a compound of Formula I*, wherein R¹ or R³ is amino(C₁-C₆)alkyl, can be reacted with methanesulfonyl chloride to give a compound of Formula I*, wherein R¹ or R³ is {methanesulfonylamino}(C₁-C₆)alkyl.
- 20 (6) a compound of Formula I*, wherein R¹ is (C₂-C₆)alkenyl, is hydroborated to afford a compound of Formula I*, wherein R¹ is hydroxy(C₂-C₆)alkyl.
- (7) a compound of Formula I*, wherein R³ is (C₂-C₆)alkenyl, is hydroborated to afford a compound of Formula I*, wherein R³ is hydroxy(C₂-C₆)alkyl.

(8) a compound of Formula I*, wherein R¹ is (C₂-C₆)alkenyl, can be reacted with osmium tetroxide and N-methylmorpholine-N-oxide to afford a compound of Formula I*, wherein R¹ is vicinal dihydroxy(C₂-C₆)alkyl.

(9) a compound of Formula I*, wherein R³ is (C₂-C₆)alkenyl, can be reacted with osmium tetroxide and N-methylmorpholine-N-oxide to afford a vicinal diol compound of Formula I*, wherein R³ is vicinal dihydroxy(C₂-C₆)alkyl.

(10) a compound of Formula I*, wherein R¹ is (C₂-C₆)alkenyl, can be reacted with ozone followed by NaBH₄ to give a compound of Formula I*, wherein R¹ is ω-hydroxy(C₁-C₅)alkyl.

(11) a compound of Formula I*, wherein R³ is (C₂-C₆)alkenyl, can be reacted with ozone followed by NaBH₄ to give a compound of Formula I*, wherein R³ is ω-hydroxy(C₁-C₅)alkyl.

(12) a compound of Formula I*, wherein R¹ or R³ is amino(C₁-C₆)alkyl, can be reacted with an (C₁-C₆)alkyl isocyanate to give a compound of Formula I*, wherein R¹ or R³ is (C₁-C₆)alkylaminocarbonylamino(C₁-C₆)alkyl.

(13) a compound of Formula I*, wherein R¹ or R³ is amino(C₁-C₆)alkyl, can be reacted with an (C₁-C₆)alkyl chloroformate to give a compound of Formula I*, wherein R¹ or R³ is (C₁-C₆)alkoxycarbonylamino(C₁-C₆)alkyl.

(14) a compound of Formula I*, wherein R¹ or R³ is amino(C₁-C₆)alkyl, can be reacted with chlorosulfonyl isocyanate or sulfamide to give a compound of Formula I*, wherein R¹ or R³ is aminosulfonylamino(C₁-C₆)alkyl.

(15) a compound of Formula I*, wherein R¹ or R³ is amino(C₁-C₆)alkyl, can be reacted with a (C₁-C₆)alkylsulfamoyl chloride to give a compound of Formula I*, wherein R¹ or R³ is (C₁-C₆)alkylaminosulfonylamino(C₁-C₆)alkyl.

(16) a compound of Formula I*, wherein R¹ or R³ is hydroxy(C₁-C₆)alkyl, can be reacted with chlorosulfonyl isocyanate to give a compound of Formula I*, wherein R¹ or R³ is aminosulfonyloxy(C₁-C₆)alkyl.

(17) a compound of Formula I*, wherein R¹ or R³ is hydroxy(C₁-C₆)alkyl, can be reacted with p-nitrophenyl chloroformate, pentafluorophenyl chloroformate or carbonyl diimidazole, followed by ammonia, a (C₁-C₆)alkylamine or a di(C₁-C₆)alkylamine to give a compound of Formula I*, wherein R¹ or R³ is aminocarboxy(C₁-C₆)alkyl, (C₁-C₆)alkyl aminocarboxy(C₁-C₆)alkyl or di(C₁-C₆)alkyl aminocarboxy(C₁-C₆)alkyl.

(18) a compound of Formula I*, wherein R¹ or R³ is hydroxy(C₁-C₆)alkyl, can be reacted with POCl₃ to give a compound of Formula I*, wherein R¹ or R³ is (HO)₂P(=O)O(C₁-C₆)alkyl.

(19) a compound of Formula I*, wherein R³ is allyl or homoallyl, can be reacted with oxygen in the presence of PdCl₂ and CuCl to afford a compound of Formula I*, wherein R³ is 2-oxopropyl or 3-oxobutyl respectively.

(20) a compound of Formula I*, wherein R^3 is 2-oxopropyl or 3-oxobutyl, can be reacted with MeMgX , wherein X is Cl, Br or I, to give a compound of Formula I*, wherein R^3 is 2-hydroxy-2-methylpropyl or 3-hydroxy-3-methylpropyl respectively.

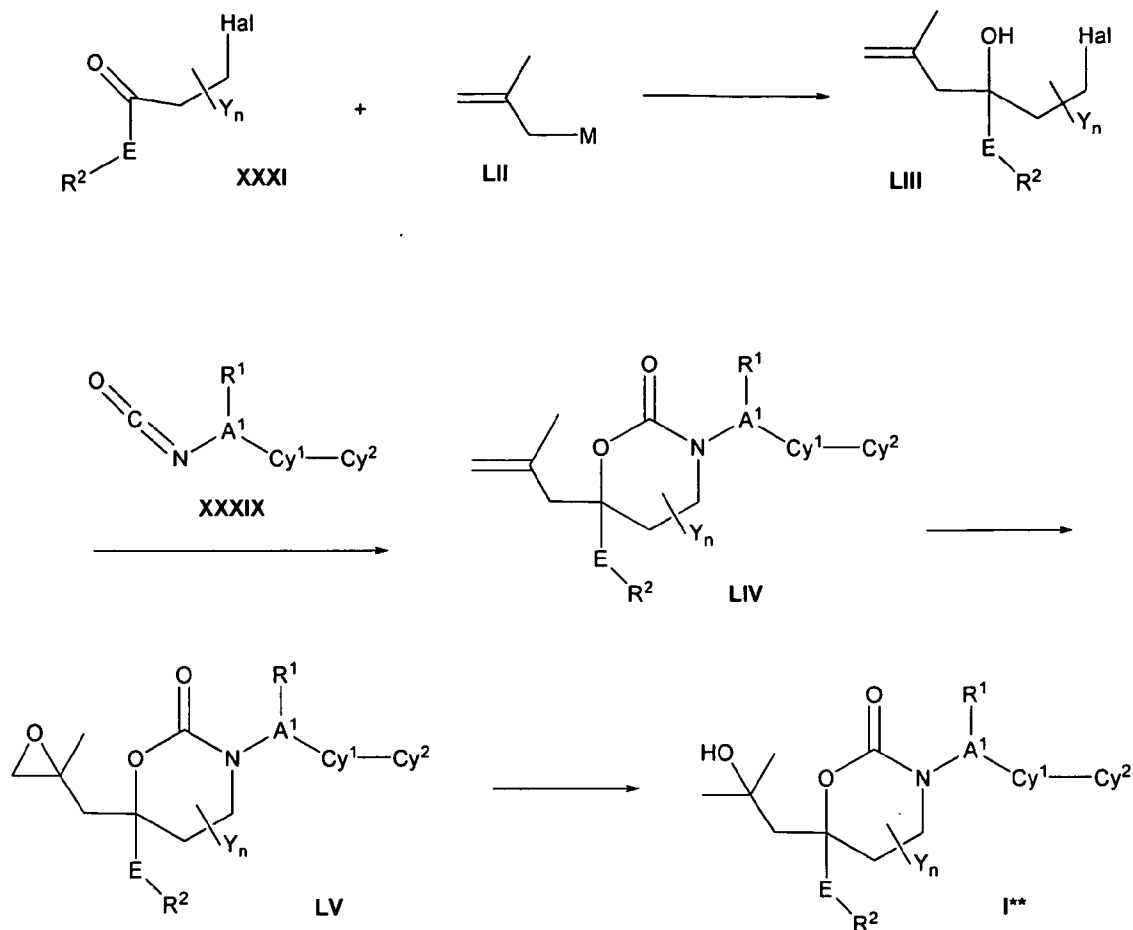
5 (21) a compound of Formula I*, wherein R^3 is $-\text{CH}_2\text{CO}_2\text{Me}$ can be treated with MeMgX , wherein X is Cl, Br or I, to give a compound of Formula I*, wherein R^3 is 2-hydroxy-2-methylpropyl.

(22) a compound of Formula I*, wherein R^3 is allyl or $-\text{CH}_2\text{C}(\text{Me})=\text{CH}_2$, can be hydrocyanated with TsCN in the presence of triphenylsilane and various cobalt catalysts to afford compounds of Formula I*, wherein R^3 is $-\text{CH}_2\text{CH}(\text{CN})\text{Me}$ or $-\text{CH}_2\text{CMe}_2\text{CN}$ respectively.

10 (23) a compound of Formula I*, wherein R^3 is $\text{CH}_2\text{C}(\text{Me})_2\text{CN}$, can be treated with acetamide in the presence of PdCl_2 to give a compound of Formula I*, wherein R^3 is $\text{CH}_2\text{CMe}_2\text{CONH}_2$.

(24) a compound of Formula I*, wherein R^3 is $-\text{CH}_2\text{C}(\text{Me})=\text{CH}_2$ can be treated with m-CPBA followed by lithium triethylborohydride to afford a compound of Formula I*, wherein R^3 is
15 2-hydroxy-2-methylpropyl.

In a tenth process, certain compounds of the invention of Formula I** are prepared as follows:

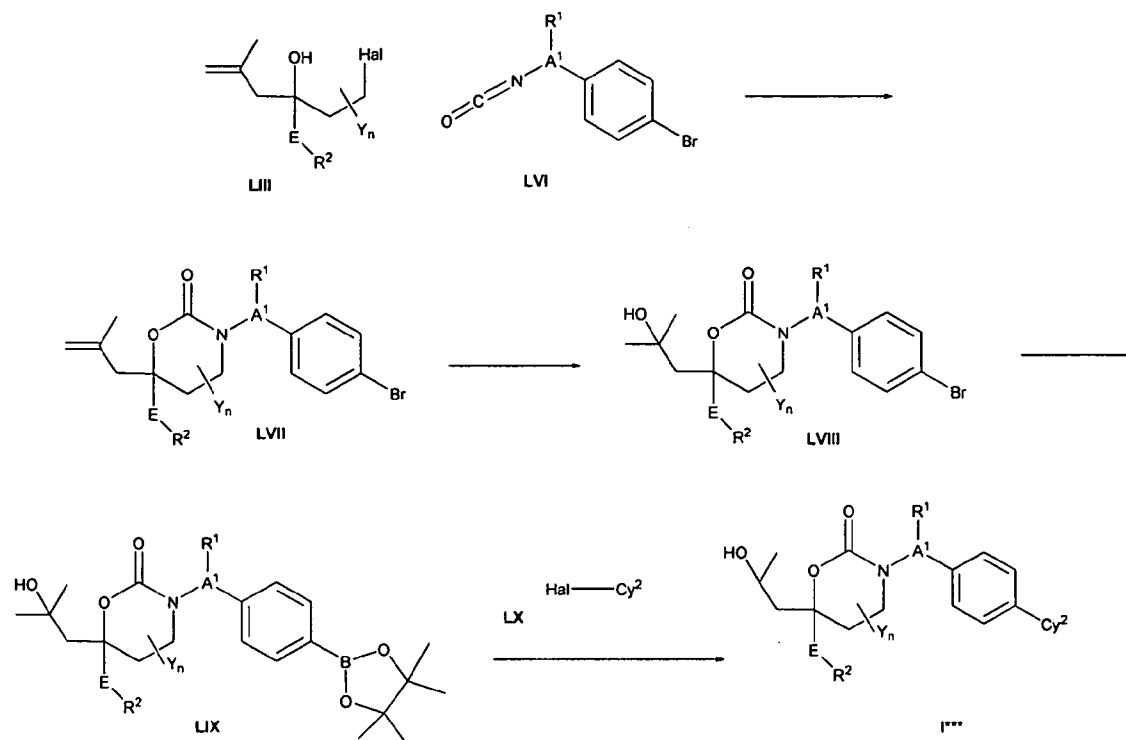


Halo compounds of Formula LIII can be formed by the treatment of β -halo ketones of Formula XXXI with organometallic reagents of Formula LII, wherein M denotes MgCl, MgBr, MgI, ZnBr or ZnI and the reaction is optionally performed in the presence of anhydrous cerium trichloride in an inert anhydrous solvent, such as tetrahydrofuran, at about -25 to 0 °C for about 0.5 h.

Cyclic carbamates of Formula LIV can be prepared from the reaction between β -haloalcohols of Formula LIII where Hal is a chloride and isocyanates of Formula XXXIX in the presence of a base, such as but not limited to DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), in a refluxing inert solvent, such as but not limited to tetrahydrofuran.

Tertiary alcohols of Formula LVII can be derived from trisubstituted alkenes of Formula LIV by first epoxidizing the alkene with an epoxidation reagent, such as m-CPBA (3-chloroperbenzoic acid), in an inert solvent, such as dichloromethane to produce the corresponding epoxides of Formula LV. The resulting epoxide is then reductively ring opened to provide the corresponding tertiary alcohol I* via treatment with a strong hydride reagent, such as lithium triethylborohydride, in an anhydrous inert solvent, such as tetrahydrofuran.

In a variation of the tenth process, a compound of the invention of Formula I*** is prepared by using a "Suzuki" coupling reaction of a boronate ester of Formula LIX with a



The boronate ester of Formula LIX is prepared by reaction of a bromide of Formula LVIII with bis(pinacolato)diboron. LVIII is prepared by epoxidation of alkene LVII, followed by reductive epoxide opening as described above, for 2-methyl-2-hydroxypropyl group is introduced via epoxidation and hydride ring opening as described above for conversion of LIV to I**.

This tenth process is described in greater detail in U.S. Provisional Application Serial No. 61/137,013, filed July 25, 2008 entitled SYNTHESIS OF INHIBITORS OF 11 β -HYDROXYSTEROID DEHYDROGENASE TYPE 1 (Attorney Docket No. 4370.1001-000), the entire teachings of which are incorporated herein by reference.

LC-MS METHODS

Method 1 [LC-MS (3 min)]

Column: Chromolith SpeedRod, RP-18e, 50 x 4.6 mm; Mobil phase: A: 0.01%TFA/water, B: 0.01%TFA/CH₃CN; Flow rate: 1 mL/min; Gradient:

Time (min)	A%	B%
0.0	90	10
2.0	10	90
2.4	10	90
2.5	90	10
3.0	90	10

Method 2 (10-80)

Column	YMC-PACK ODS-AQ , 50×2.0mm 5μm		
Mobile Phase	A: water (4 L) + TFA (1.5 mL)		
	B: acetonitrile (4 L) + TFA (0.75 mL)		
	TIME(min)	A%	B%
	0	90	10
	2.2	20	80
	2.5	20	80
Flow Rate	1mL/min		
Wavelength	UV 220 nm		
Oven Temp	50 °C		
MS ionization	ESI		

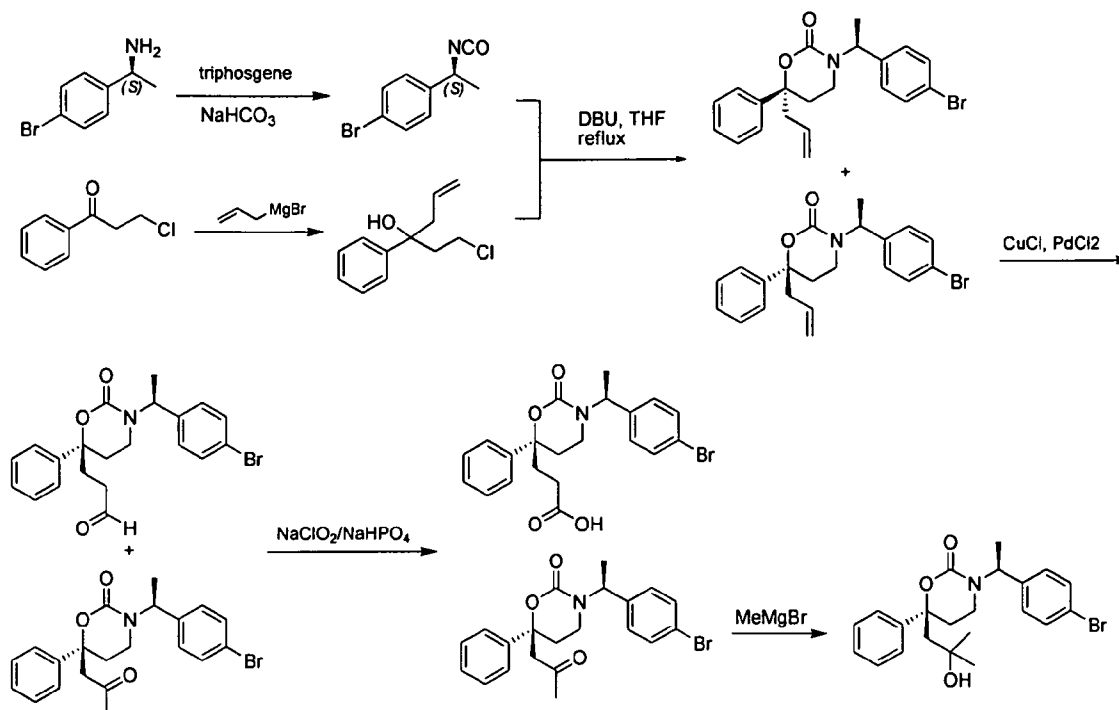
5 Method 3 (30-90)

Column	YMC-PACK ODS-AQ , 50×2.0mm 5μm		
Mobile Phase	A: water (4 L) + TFA (1.5 mL)		
	B: acetonitrile (4 L) + TFA (0.75 mL)		
	TIME(min)	A%	B%
	0	70	30
	2.2	10	90
	2.5	10	90
Flow Rate	1 mL/min		
Wavelength	UV220		
Oven Temp	50 °C		
MS ionization	ESI		

PREPARATION 1

10 (S)-3-((S)-1-(4-bromophenyl)ethyl)-6-(2-hydroxy-2-methylpropyl)-6-phenyl-1,3-oxazinan-2-one

Method 1



Step 1: (S)-1-bromo-4-(1-isocyanatoethyl)benzene

To a solution of (S)-1-(4-bromophenyl)ethanamine (240 g, 1.2 mol) in methylene chloride (3 L) and satd aq NaHCO₃ (3 L) solution was added triphosgene (118 g, 0.396 mol) at 0 °C. The mixture was stirred for 15 min. The organic phase was separated, dried over Na₂SO₄ and concentrated to give 1-bromo-4-(1-isocyanato-ethyl) -benzene (170 g, 63%).

Step 2: 1-chloro-3-phenylhex-5-en-3-ol

To a solution of 3-chloro-1-phenylpropan-1-one (170 g, 1.01 mol) in anhydrous THF (1200 mL) was added allylmagnesium bromide (1.2 L, 1mol/L) at -78 °C under nitrogen. The formed mixture was stirred for 30 min at -78 °C. The reaction was quenched with aqueous NaHCO₃ solution. The organic phase was separated, dried over Na₂SO₄ and concentrated to give the crude product, which was purified by column chromatography (petroleum ether/EtOAc=100:1) to afford 1-chloro-3-phenylhex-5-en-3-ol (180 g, 86%). ¹H NMR (CDCl₃): 2.27 (m, 2H), 2.51 (m, 1H), 2.74 (m, 1H), 3.22 (m, 1H), 3.58 (m, 1H), 5.16 (m, 2H), 5.53 (m, 1H), 7.23 (m, 1H), 7.39 (m, 4H).

Step 3: (R)-6-allyl-3-((S)-1-(4-bromophenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one

A mixture of 1-chloro-3-phenyl-hex-5-en-3-ol (105 g, 0.050 mmol), (S)-(-)-1-(4-bromophenyl)ethyl isocyanate (170 g, 0.752 mol), and DBU (228 g, 1.5 mol) in THF (1700 mL)

was heated to reflux overnight. The mixture was diluted with EtOAc and washed with 1N aq HCl. The aqueous phase was extracted with EtOAc (3 x). The combined organic phase was dried over Na₂SO₄. After the solvents were evaporated, the crude product was purified by column chromatography (petroleum ether/EtOAc =20:1 to 5:1) to give (R)-6-allyl-3-((S)-1-(4-bromophenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one (100 g, 34 %). ¹H NMR (CDCl₃): 1.39 (d, 3H), 2.14 (m, 1H), 2.24 (m, 2H), 2.48-2.61 (m, 3H), 2.82 (m, 2H), 5.01 (m, 2H), 5.52 (q, 1H), 5.73 (m, 1H), 6.62 (d, 2H), 7.12 (m, 2H), 7.28 (m, 2H).

Step 4: (S)-3-((S)-1-(4-bromophenyl)ethyl)-6-(2-oxopropyl)-6-phenyl-1,3-oxazinan-2-one and 3-((R)-3-((S)-1-(4-bromophenyl)ethyl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)propanal

To a solution of (R)-6-allyl-3-((S)-1-(4-bromophenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one (31 g, 78 mmol) and CuCl (19.3 g, 195 mmol) in dry DMF (150 mL) was added H₂O (50 mL) and PdCl₂ (4.10 g, 23 mmol) at rt. After addition, the mixture was stirred overnight under oxygen. After TLC showed the starting material had disappeared, the solid was filtered off. Water (200 mL) and EtOAc (200 mL) was added, the organic layers were separated and the aqueous layer was extracted with EtOAc (3 x 40 mL). The combined organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated to give a residue which was purified by column chromatography (petroleum ether/EtOAc =5:1 to 1:1) to give a mixture of (S)-3-((S)-1-(4-bromophenyl)ethyl)-6-(2-oxopropyl)-6-phenyl-1,3-oxazinan-2-one and 3-((R)-3-((S)-1-(4-bromophenyl)ethyl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)propanal, (26 g, 81%).

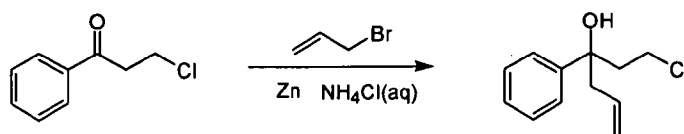
Step 5: (S)-3-((S)-1-(4-bromophenyl)ethyl)-6-(2-oxopropyl)-6-phenyl-1,3-oxazinan-2-one

To a mixture of (S)-3-((S)-1-(4-bromophenyl)ethyl)-6-(2-oxopropyl)-6-phenyl-1,3-oxazinan-2-one and 3-((R)-3-((S)-1-(4-bromophenyl)ethyl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)propanal (20 g, 48.2 mmol) in t-BuOH (250 mL) and 2-methyl-2-butene (50 mL) was added a solution of NaClO₂ (19.3 g, 0.213 mol) and NaH₂PO₄ (28 g, 0.179 mol) in H₂O (300 mL) at 0 °C. The formed mixture was stirred for 1 h at 0 °C. The mixture was treated with water (100 mL) and extracted with CH₂Cl₂. The combined organic layer was dried over Na₂SO₄, filtered and concentrated to leave a residue, which was purified by column chromatography (petroleum ether/EtOAc =5:1 to 2.5:1) to afford (S)-3-((S)-1-(4-bromophenyl)ethyl)-6-(2-oxopropyl)-6-phenyl-1,3-oxazinan-2-one (10.0 g, 83%). ¹H NMR (CDCl₃): 1.49 (d, 3H), 2.12 (s, 3H), 2.33 (m, 2H), 2.63 (m, 1H), 2.86-3.08 (m, 3H), 5.57 (q, 1H), 6.66 (d, 2H), 7.19 (m, 2H), 7.33 (m, 5H).

Step 6: (S)-3-((S)-1-(4-bromophenyl)ethyl)-6-(2-hydroxy-2-methylpropyl)-6-phenyl-1,3-oxazinan-2-one

To a solution of (S)-3-((S)-1-(4-bromophenyl)ethyl)-6-(2-oxopropyl)-6-phenyl-1,3-oxazinan-2-one (20 g, 46.4 mmol) in anhydrous THF (200 mL) was added dropwise methylmagnesium bromide (31 mL, 144 mmol) at -78 °C under nitrogen. Then the mixture was stirred at rt for 1 h. The reaction mixture was quenched with aq NaHCO₃ (50 mL) under ice water bath. The organic layers were separated. The aqueous layer was extracted with EtOAc (150 mL). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated in *vacuo* to give the crude product, which was purified column chromatography (petroleum ether/EtOAc =5:1 to 2:1) to afford (S)-3-((S)-1-(4-bromophenyl)ethyl)-6-(2-hydroxy-2-methylpropyl)-6-phenyl-1,3-oxazinan-2-one (13 g, 65%). After re-crystallization from EtOH, 4 g of the pure compound was obtained. ¹H NMR (CDCl₃): 1.06 (s, 3H), 1.12 (s, 3H), 1.44 (d, 3H), 2.14 (m, 3H), 2.21 (m, 1H), 2.33 (m, 1H), 2.76 (m, 1H), 5.54 (q, 1H), 6.74 (d, 2H), 7.16 (d, 2H), 7.28 (m, 5H).

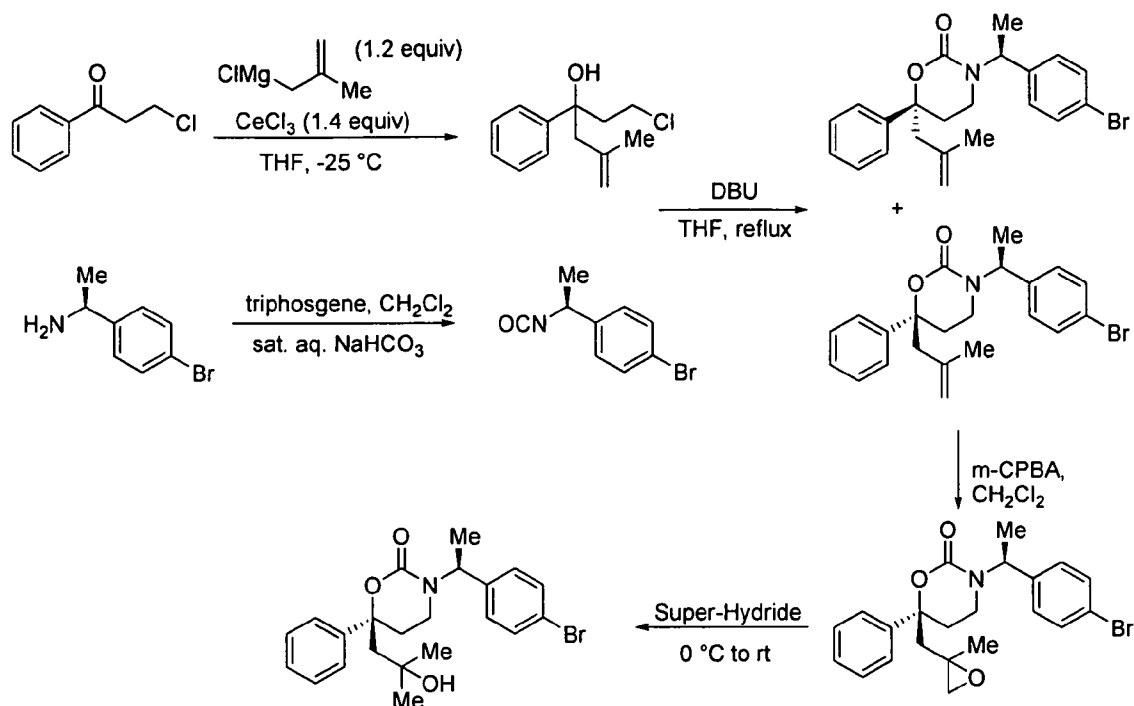
Alternative Procedure for Method 1 Step 2



A solution of 3-chloro-1-phenylpropan-1-one (100 g, 0.595 mol) in THF (280 ml) was added dropwise to a well-stirred mixture of zinc powder (need not be activated) (40 g, 1.231 mol, satd aq NH₄Cl solution (1500 ml) and THF (400 ml). Allyl bromide (143 g, 1.19 mol) was dissolved in THF (200 ml) was slowly added to the reaction mixture. The reaction was mildly exothermic, and the mixture began to reflux spontaneously. After refluxing had ceased, the mixture was stirred for 1 h. The mixture was extracted with EtOAc, dried over anhydrous Na₂SO₄, and concentrated to give 1-chloro-3-phenylhex-5-en-3-ol (122 g, 97%). ¹H NMR: (400MHz, CDCl₃): δ=2.24(s, 1H), 2.34 (m, 2H), 2.53 (m, 1H), 2.75 (m, 1H), 3.20 (m, 1H), 3.58 (m, 1H), 5.18 (t, 1H), 5.51 (m, 1H), 7.26 (m, 1H), 7.26-7.39 (m, 3H).

(R)-6-allyl-3-((S)-1-(4-bromophenyl)propyl)-6-phenyl-1,3-oxazinan-2-one was prepared from (S)-1-(4-bromophenyl)propan-1-amine following procedures analogous to those described in Preparation 1 Method 1 Steps 1 to 3 above.

(S)-3-((S)-1-(4-bromophenyl)ethyl)-6-(4-fluorophenyl)-6-(2-hydroxy-2-methylpropyl)-1,3-oxazinan-2-one was prepared from (R)-6-allyl-3-((S)-1-(4-bromophenyl)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one following procedures analogous to those described in Preparation 1 Method 1 Steps 4 and 6.

Method 2

Step 1. 1-Chloro-5-methyl-3-phenyl-hex-5-en-3-ol

- 5 To a stirred suspension of magnesium turnings (46.7 g, 1.94 mol) in 1500 mL of THF (H_2O <100 ppm based on Karl Fischer titration) was charged 53.0 mL of 1 M DIBAL-H in hexane under nitrogen at rt. Then 3-chloro-2-methylprop-1-ene (160 g, 1.77 mol) was introduced while maintaining the internal temperature below 30 °C. The resulting solution was agitated for 2 h at rt. The solution was titrated in the presence of 1,1'-bipyridine to indicate 0.8 M of the corresponding
- 10 Grignard reagent. To a dry flask containing 307.0 g of anhydrous CeCl_3 (1.25 mol) at rt under nitrogen was added 1556.8 mL of the Grignard reagent (0.8 M, 1.25 mol). The resulting slurry was cooled to -10 °C and agitated for 0.5 h. To the slurry was added 200 g of 3-chloro-1-phenylpropan-1-one (1.19 mol) in 200 mL of THF while maintaining the internal temperature below 0 °C. After the mixture was stirred for 0.5 h, 1200 mL of 1 M aq HCl was added to obtain a
- 15 clear solution while maintaining the internal temperature below 30 °C. After the phase cut, the aqueous layer was extracted with EtOAc (500 mL). The combined organic layers were washed with brine and dried over sodium sulfate. Removal of the solvent under vacuum produced crude 1-chloro-5-methyl-3-phenyl-hex-5-en-3-ol, which was chased with THF to achieve H_2O <500 ppm based on Karl Fischer titration. The crude product (306 g, 83wt%, 95% yield) was used directly in
- 20 Step 3. ^1H -NMR spectroscopy (500 MHz, CDCl_3) δ 7.38-7.37 (d, J = 7.8 Hz, 2H), 7.33 (t, J = 7.9 Hz, 2H), 7.24 (t, J = 7.4 Hz, 1 H), 4.91 (s, 1H), 4.76 (s, 1H), 3.57 (ddd, J = 5.6, 10.7, and 10.7, 1H), 3.13 (ddd, J = 4.7, 10.7 and 10.7 Hz, 1H), 2.66 (d, J = 13.3 Hz, 1H), 2.54 (d, J = 11.3 Hz, 1H), 2.53

(s, 1H), 2.36 (ddd, $J = 5.4, 10.6$ and 13.9 Hz, 1H), 2.29 (ddd, $J = 5.6, 11.3$ and 13.3 Hz, 1H), 1.29 (s, 3H). ^{13}C -NMR spectroscopy (125 MHz, CDCl_3) δ 144.3, 141.4, 128.0, 126.6, 124.8, 116.1, 74.2, 51.2, 46.0, 39.9, 23.9.

5 Step 2. 1-Bromo-4-((S)-1-isocyanato-ethyl)-benzene

To a 10 L jacketed reactor was charged 241 g of sodium bicarbonate (2.87 mol, 2.30 equiv) and 5 L of deionized water. The resulting solution was agitated for 10-20 min, until the solids dissolved (homogeneous). To the clear solution was charged 250 g (1.25 mol, 1.00 equiv) of (S)-(-)-1-(4-bromophenyl)ethylamine as a solution in 1.00 L of dichloromethane. An additional 4
10 L of dichloromethane was charged to the reactor. The biphasic solution was agitated and cooled to $T_{\text{int}} = 2-3$ °C. Triphosgene (126 g, 424 mmol, 0.340 equiv) was charged to the reactor in approximately two equal portions ~ 6 min apart. It should be noted that a slight exotherm was noted upon the addition of triphosgene. The resulting murky solution was agitated at $T_{\text{int}} = 2-5$ °C for 30 min, at which point HPLC analysis indicates >99 A% conversion (220 nm). The
15 dichloromethane layer was cut and dried with anhydrous sulfate. The resulting solution was passed through a celite plug and concentrated to ~1.5 L which fine particles of a white solid developed. The solution was filtered and concentrated to a thick oil via reduced pressure to produce 239 g of 1-bromo-4-((S)-1-isocyanato-ethyl)-benzene (93.7 wt%, 79.4 % yield). ^1H -NMR spectroscopy (400 MHz, CD_2Cl_2) δ 7.53 (d, $J = 11.4$ Hz, 2 H), 7.26 (d, $J = 8.2$ Hz, 2 H), 4.80 (q, $J =$
20 6.7 Hz, 1H), 1.59 (d, $J = 6.7$ Hz, 3 H). The material was used in Step 3 without further purification.

Step 3. (R)-3-((S)-1-(4-bromophenyl)ethyl)-6-(2-methylallyl)-6-phenyl-1,3-oxazinan-2-one

To a dried 10 L jacketed reactor under a nitrogen atmosphere was charged 1-chloro-5-methyl-3-phenyl-hex-5-en-3-ol (167 g, 81.7 wt%, 610 mmol, 1.00 equiv), 1-bromo-4-((S)-1-isocyanato-ethyl)-benzene (219 g, 93.7 wt%, 911 mmol, 1.50 equiv), anhydrous tetrahydrofuran (3.00 L), and then 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 409 mL, 2.73 mol, 4.50 equiv). The resulting solution was agitated and refluxed ($T_{\text{int}} = 67-69$ °C, $T_{\text{ext}} = 75$ °C) for 19 h, at which point HPLC analysis indicated ~ 1A% (220 nm) of the 1-chloro-5-methyl-3-phenyl-hex-5-en-3-ol remained. The dark solution was cooled to $T_{\text{int}} = 20-25$ °C. Two liters of tetrahydrofuran were
30 removed by distillation under reduced pressure. The remaining dark solution was diluted with 4.0 L of ethyl acetate and 1.0 L of hexanes. The resulting solution was washed with 4.0 L of a 1.0 M aqueous solution of hydrogen chloride (note: the wash is slightly exothermic). The aqueous solution was cut and the remaining organic solution was dried with anhydrous sodium sulfate, filtered and then concentrated to an oil via reduced pressure. The resulting material was
35 subjected to flash silica chromatography (5-30 % ethyl acetate/hexanes, 1.74 kg of silica) to produce 137.8 g of material (59 wt%, 3.1:1 diastereomeric ratio favoring the desired diastereomer

(R)-3-((S)-1-(4-bromophenyl)ethyl)-6-(2-methylallyl)-6-phenyl-1,3-oxazinan-2-one, 32.3 % yield). The material was used in Step 4 without further purification.

Analytical data for (R)-3-((S)-1-(4-bromophenyl)ethyl)-6-(2-methylallyl)-6-phenyl-1,3-oxazinan-2-one: ¹H-NMR spectroscopy (500 MHz, CD₂Cl₂) δ 7.42-7.35 (m, 3 H), 7.33-7.31 (m, 2H), 7.25-7.23 (m, 2H), 6.80-6.74 (m, 2), 5.55 (q, J= 7.1 Hz, 1 H), 5.37-5.36 (m, 1H), 4.89 (s, 1H), 4.69 (s, 1H), 2.96-2.93 (m, 1H), 2.61 (dd, J= 13.8 and 26.4 Hz, 2 H), 2.37-2.25 (m, 3H), 1.68 (s, 3H), 1.50 (d, J= 7.1 Hz, 3 H). ¹³C-NMR spectroscopy (125 MHz, CD₂Cl₂) δ 152.5, 141.5, 140.1, 138.3, 130.6, 128.1, 128.0, 126.9, 124.4, 120.2, 115.3, 82.4, 52.1, 50.1, 35.6, 29.8, 23.4, 14.5.

Analytical data for (S)-3-((S)-1-(4-bromophenyl)ethyl)-6-(2-methylallyl)-6-phenyl-1,3-oxazinan-2-one: ¹H-NMR spectroscopy (400 MHz, CD₂Cl₂) δ 7.50-7.48 (m, 2H), 7.43-7.39 (m, 2H), 7.35-7.32 (m, 3H), 7.20-7.18 (m, 2H), 5.60 (q, J= 7.1 Hz, 1H), 4.85 (s, 1H), 4.66 (s, 1H), 2.73-2.67 (m, 2H), 2.60 (dd, J= 13.9 and 19.4 Hz, 2H), 2.28 (dt, J= 3.3 and 13.7 Hz, 1H), 2.14-2.05 (m, 1H), 1.66 (s, 3H), 1.24 (d, J= 7.2 Hz, 3 H). ¹³C-NMR spectroscopy (100 MHz, CD₂Cl₂) δ 153.4, 142.5, 141.0, 140.1, 131.8, 129.3, 128.9, 127.8, 125.3, 121.5, 116.3, 83.9, 53.2, 51.0, 36.6, 31.3, 24.3, 15.4.

Step 4. (6S)-3-((S)-1-(4-bromophenyl)ethyl)-6-((2-methyloxiran-2-yl)methyl)-6-phenyl-1,3-oxazinan-2-one

To a 1.0 L 2-neck RBF was charged (R)-3-((S)-1-(4-bromophenyl)ethyl)-6-(2-methylallyl)-6-phenyl-1,3-oxazinan-2-one (135.8 g, 59 wt%, 3.1:1 dr, 193 mmol, 1.00 equiv), dichloromethane (700 mL), and then 3-chloroperbenzoic acid (m-CPBA, 70%, 95.3 g, 386 mmol, 2.0 equiv). The resulting solution was agitated at rt (T_{int}=20-25 °C) for 1 h, which HPLC analysis indicates >99 A% (220 nm) conversion. The resulting solution was diluted with 700 mL of methyl *tert*-butyl ether (MTBE) and washed with 1x500 mL of 30 wt% solution of sodium thiosulfate and 1x500 mL of saturated aqueous solution of sodium bicarbonate. The wash sequence was repeated until the peak on an HPLC trace of the organic solution that corresponds to a HPLC sample peak of m-CPBA is <2.5 A% (220 nm), which in this example the wash sequence was repeated 3 times. The resulting organic layer was dried with anhydrous sodium sulfate, filtered and then concentrated to an oil via reduced pressure. The resulting material was diluted with 200 mL of anhydrous tetrahydrofuran and then concentrated to a thick oil via reduced pressure to provide (6S)-3-((S)-1-(4-bromophenyl)ethyl)-6-((2-methyloxiran-2-yl)methyl)-6-phenyl-1,3-oxazinan-2-one which was used directly in Step 5.

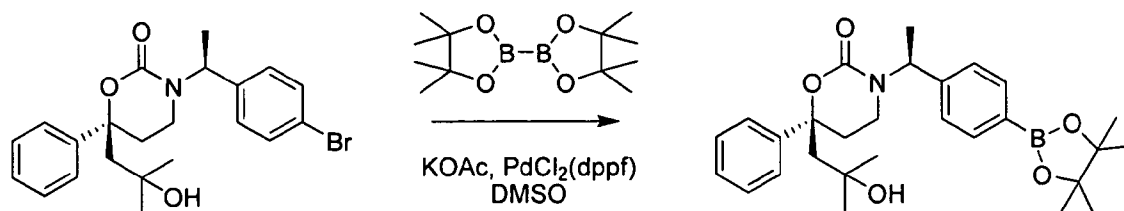
Step 5. (S)-3-((S)-1-(4-bromophenyl)ethyl)-6-(2-hydroxy-2-methylpropyl)-6-phenyl-1,3-oxazinan-2-one

To a 2.0 L 3-neck oven-dried RBF was charged the crude (6S)-3-((S)-1-(4-bromophenyl)ethyl)-6-((2-methyloxiran-2-yl)methyl)-6-phenyl-1,3-oxazinan-2-one and 750 mL of

anhydrous THF. The resulting solution was agitated and cooled to $T_{int} = 2-3\text{ }^{\circ}\text{C}$. To the agitated clear solution was charged 1.0 M lithium triethylborohydride in tetrahydrofuran (Super Hydride, 348 mL, 348 mmol, 1.8 equiv). The addition is exothermic and addition was controlled to maintain $T_{int} < 8\text{ }^{\circ}\text{C}$. The resulting solution was agitated at $T_{int} = 2-3\text{ }^{\circ}\text{C}$ for 1.5 h and then allowed to warm to $T_{int} = 10-13\text{ }^{\circ}\text{C}$ over a 2.5 h, which HPLC analysis indicates ~94 A% (220 nm) conversion. To the agitated solution was charged a solution of hydrogen peroxide (95.7 mL of a 35 wt% aqueous solution diluted with 400 mL of water, 1.08 mol, 5.60 equiv). The addition is *highly exothermic* and addition was controlled to maintain $T_{int} < 25\text{ }^{\circ}\text{C}$. The resulting solution was diluted with 1.00 L of methyl *tert*-butyl ether (MTBE) and washed with 1.00 L of water followed by 500 mL of a ~30 wt% solution of sodium thiosulfate. The organic solution was dried with anhydrous sodium sulfate, filtered, and then concentrated via reduced pressure. The resulting material was subjected to flash silica chromatography (10-60% ethyl acetate, 600 g of silica) to produce 68 g of material consisting of both diastereomers (1.98:1 dr) and 41 g of the desired diastereomer, (>99:1 dr). The material consisting of the mixed fractions was recrystallized from 250 mL of isopropyl acetate (IPAC) and 200 mL of heptane (anti-solvent) to produce upon filtration 31.3 g of product (95.7 A% at 220 nm, 74:1 dr). The two samples were combined to produce 72.3 g of (S)-3-((S)-1-(4-bromophenyl)ethyl)-6-(2-hydroxy-2-methylpropyl)-6-phenyl-1,3-oxazinan-2-one (83.6 % yield for the two step operation). $^1\text{H-NMR}$ spectroscopy (400 MHz, CDCl_3) δ 7.37-7.29 (m, 5H), 7.25-7.21 (m, 2H), 6.82-6.79 (m, 2H), 5.61 (q, $J = 6.9\text{ Hz}$, 1H), 2.83 (ddd, $J = 2.5, 5.4\text{ and }11.6\text{ Hz}$, 1H), 2.39 (ddd, $J = 5.7, 12.0\text{ and }14.1\text{ Hz}$, 1H), 2.27 (ddd, $J = 2.6, 4.8\text{ and }14.0\text{ Hz}$, 1H), 2.21-2.14 (m, 3H), 2.08 (s, 1H), 1.49 (d, $J = 7.0\text{ Hz}$, 3H), 1.18 (s, 3H), 1.13 (s, 3H). $^{13}\text{C-NMR}$ spectroscopy (100 MHz, CDCl_3) δ 153.2, 142.6, 138.5, 131.6, 129.13, 129.10, 128.0, 125.3, 121.6, 84.2, 71.4, 54.1, 53.3, 36.4, 33.6, 32.1, 30.8, 15.6.

PREPARATION 2

(S)-6-(2-hydroxy-2-methylpropyl)-6-phenyl-3-((S)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborol-2-yl)phenyl)ethyl)-1,3-oxazinan-2-one



To a solution of (S)-3-((S)-1-(4-bromophenyl)ethyl)-6-(2-hydroxy-2-methylpropyl)-6-phenyl-1,3-oxazinan-2-one (6.6 g, 15.2 mmol) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (6.1g, 24.3 mmol) in dry DMSO (20 mL) was added KOAc (4.8 g, 48.6 mmol) and Pd(dppf)Cl_2 (372 mg, 0.46 mmol). After addition, the mixture was allowed to warm to $100\text{ }^{\circ}\text{C}$ for

20 h. After TLC showed the starting material had disappeared, the solid was filtered off. Water (60 mL) and EtOAc (20mL) were added. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated to give a residue, which was purified by column chromatography to give (S)-6-(2-hydroxy-2-methylpropyl)-6-phenyl-3-((S)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl)-1,3-oxazinan-2-one (4.4 g, 60%).

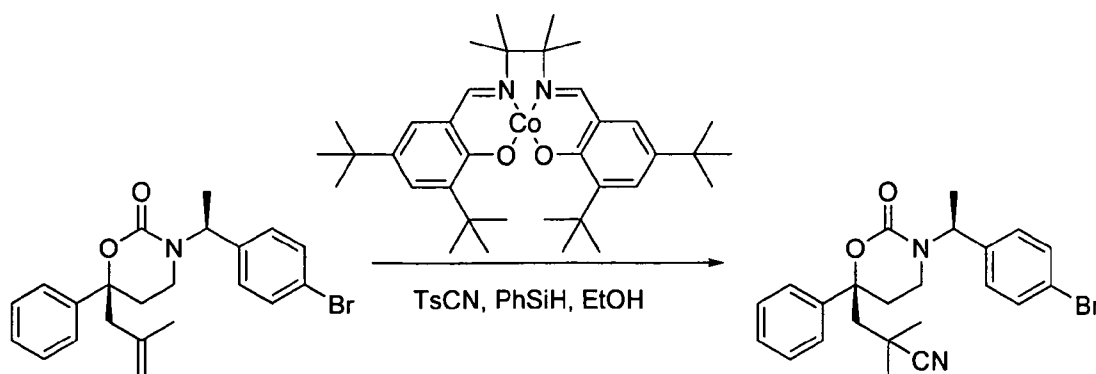
(S)-6-(4-fluorophenyl)-6-(2-hydroxy-2-methylpropyl)-3-((S)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl)-1,3-oxazinan-2-one was prepared from (S)-3-((S)-1-(4-bromophenyl)ethyl)-6-(2-hydroxy-2-methylpropyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one following an analogous procedure.

(S)-6-(2-hydroxy-2-methylpropyl)-6-phenyl-3-((S)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propyl)-1,3-oxazinan-2-one was prepared from (S)-3-((S)-1-(4-bromophenyl)propyl)-6-(2-hydroxy-2-methylpropyl)-6-phenyl-1,3-oxazinan-2-one following an analogous procedure.

(R)-6-Methoxymethyl-6-phenyl-3-((S)-1-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-ethyl)-[1,3]oxazinan-2-one was prepared from 3-[1-(4-bromo-phenyl)-ethyl]-6-methoxymethyl-6-phenyl-[1,3]oxazinan-2-one following an analogous procedure.

PREPARATION 3

3-((R)-3-((S)-1-(4-bromophenyl)ethyl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)-2,2-dimethylpropanenitrile



Preparation of Cobalt(II) Complex

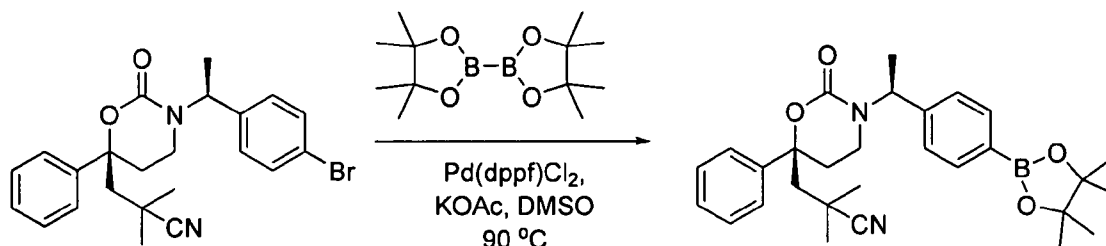
A 50 mL flask was charged with *N,N'*-bis(3,5-di-*tert*-butylsalicylidene)-1,1,2,2-tetramethylethylenediamine (0.430 g, 0.78 mmol, 1.0 equiv), EtOH (17 mL), and Co(OAc)₂ (0.139 g, 0.78 mmol, 1.0 equiv). The mixture was degassed and then heated to reflux under nitrogen for

3 h, cooled to room temperature. The precipitate was filtered and the purple solid was washed with EtOH (10 mL) and dried under high vacuum to give 0.353 g (75%) of the cobalt(II) complex.

A mixture of (R)-3-((S)-1-(4-bromophenyl)ethyl)-6-(2-methylallyl)-6-phenyl-1,3-oxazinan-2-one (490 mg, 1.18 mmol), the cobalt(II) complex whose preparation is described immediately above (8 mg, 0.01 equiv), TsCN (257 mg, 1.2 equiv), and PhSiH₃ (137 mg, 157 μ L, 1.07 equiv) in ethanol (10 mL) was stirred 4 h at rt. After removing the solvent under reduced pressure, the residue was purified by chromatography on a 40g silica gel column, eluted with a 25-80% EtOAc in hexanes gradient to afford 3-((R)-3-((S)-1-(4-bromophenyl)ethyl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)-2,2-dimethylpropanenitrile (267 mg, 51% yield). LC-MS (3min. method) t_R = 1.89min., m/z 441, 443 (M+1)

PREPARATION 4

2,2-dimethyl-3-((R)-2-oxo-6-phenyl-3-((S)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl)-1,3-oxazinan-6-yl)propanenitrile



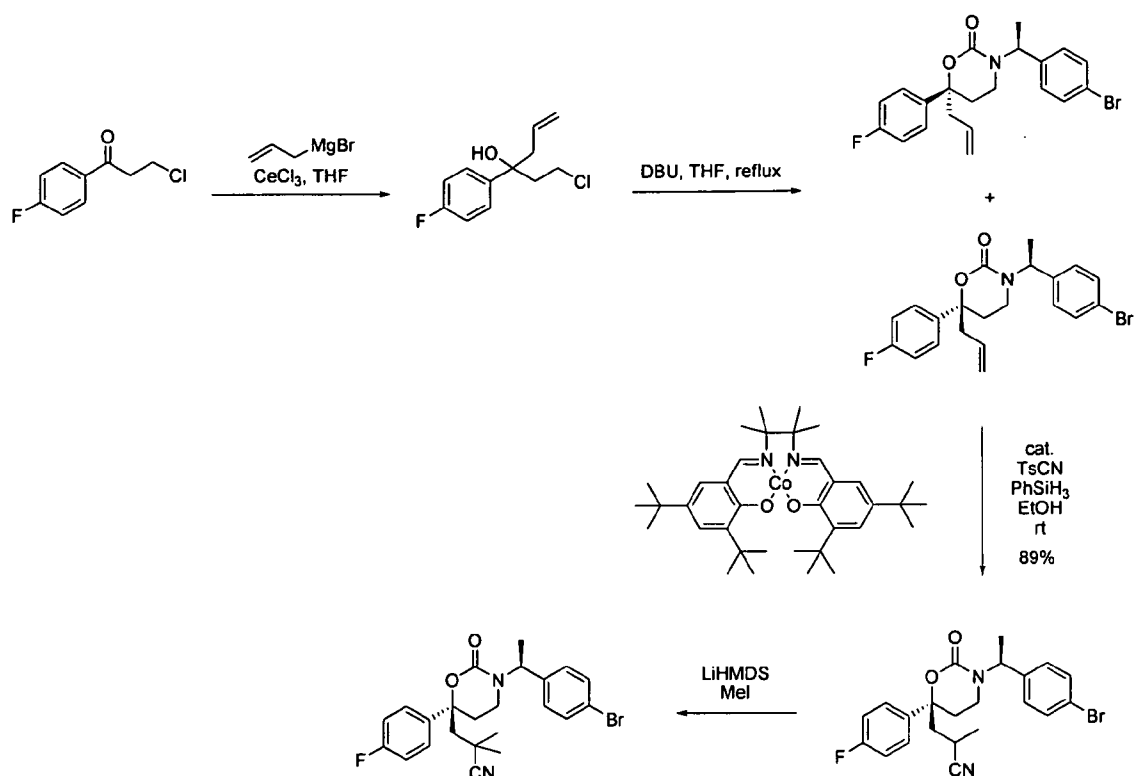
3-((R)-3-((S)-1-(4-bromophenyl)ethyl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)-2,2-dimethylpropanenitrile (467 mg, 1.06 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (538mg, 2equiv), KOAc (333mg, 3.2 equiv), PdCl₂(dppf)CH₂Cl₂ (27 mg, 0.033 equiv) were mixed with dry DMSO (6 mL). The mixture was degassed and refilled with N₂ gas 3 times. The mixture was then heated overnight at 90 °C under protection of N₂ gas. After being cooled to rt, the mixture was diluted with EtOAc (30 mL), washed with water (20 mL). The aqueous layer was extracted with EtOAc (2 x 15 mL). The combined organic layers were washed by water (15 mL), brine (2 x 10 mL) and dried over Na₂SO₄. After filtration and concentration, the residue was purified chromatography on a 40g silica gel column, eluted with a 20-50% EtOAc in Hexanes gradient, to afford 2,2-dimethyl-3-((R)-2-oxo-6-phenyl-3-((S)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl)-1,3-oxazinan-6-yl)propanenitrile (393 mg, 76% yield).

PREPARATION 5

3-((R)-3-((S)-1-(4-bromophenyl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)-2-methylpropanenitrile

Method 1

5



Step 1. 1-chloro-3-(4-fluorophenyl)hex-5-en-3-ol

10 A 250-mL flask was charged with anhydrous CeCl_3 (5.58 g, 22.6 mmol) and THF (40 mL). The mixture was vigorously stirred for 3.5 h at rt. The suspension was then cooled to -78°C and a solution of allylmagnesium bromide (1.0 M in THF, 21 mL, 21.0 mmol) was added. After stirring for 2 h at -78°C , a solution of 3-chloro-1-(4-fluorophenyl)propan-1-one (2.522 g, 13.5 mmol) in THF (30 mL) was added via cannula. The reaction mixture was allowed to slowly warm to 8°C while stirring overnight (18 h). The reaction was then quenched with satd aq NaHCO_3 ,
 15 extracted with EtOAc, and dried over Na_2SO_4 . After the solvents were evaporated, the residue was purified by chromatography on silica gel eluted with hexanes/EtOAc to afford of 1-chloro-3-(4-fluorophenyl)hex-5-en-3-ol (3.0049 g, 97%) as an oil. LC-MS Method 1 $t_R = 1.79$ min, m/z 213, 211 ($\text{M}-\text{OH}^+$); ^1H NMR (400 MHz, CDCl_3) δ 7.37-7.32 (m, 2H), 7.07-7.02 (m, 2H), 5.57-5.47 (m, 1H), 5.20-5.19 (m, 1H), 5.16 (m, 1H), 3.59-3.52 (m, 1H), 3.24-3.18 (m, 1H), 2.70 (dd, $J = 13.8$,

5.9 Hz, 1H), 2.50 (dd, $J = 13.8, 8.5$ Hz, 1H), 2.29 (t, $J = 7.9$ Hz, 2H), 2.22 (s, 1H); ^{19}F NMR (376 MHz, CDCl_3) δ -116.52 (m).

Step 2. (*R*)-6-allyl-3-((*S*)-1-(4-bromophenyl)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one and (*S*)-6-allyl-3-((*S*)-1-(4-bromophenyl)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one.

A mixture of 1-chloro-3-(4-fluorophenyl)hex-5-en-3-ol (0.4129 g, 1.8 mmol, 1.0 equiv), (*S*)-(-)-1-(4-bromophenyl)ethyl isocyanate (0.5005 g, 2.2 mmol, 1.2 equiv), and DBU (0.7375 g, 4.8 mmol, 2.7 equiv) in THF (10 mL) was heated to reflux for 25 h. The mixture was diluted with EtOAc and washed with 1 *N* aq HCl. The aqueous phase was extracted with EtOAc (2 x). The combined organic phase was dried over Na_2SO_4 . After the solvents were evaporated, the crude product was directly used in the next step without further purification.

An analytical sample was purified by chromatography on silica gel eluted with hexanes/EtOAc to afford the two diastereomers of 6-allyl-3-((*S*)-1-(4-bromophenyl)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one.

Isomer 1: (*S*)-6-allyl-3-((*S*)-1-(4-bromophenyl)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one. LC-MS Method 1 $t_R = 2.03$ min, m/z 420, 418 (MH^+); ^1H NMR (400 MHz, CDCl_3) δ 7.46 (d, $J = 8.2$ Hz, 2H), 7.31-7.28 (m, 2H), 7.17 (d, $J = 8.2$ Hz, 2H), 7.07 (t, $J = 8.5$ Hz, 2H), 5.76-5.66 (m, 2H), 5.10-4.99 (m, 2H), 2.75-2.52 (m, 4H), 2.23-2.19 (m, 1H), 2.08-2.00 (m, 1H), 1.24 (d, $J = 7.0$ Hz, 3H); ^{19}F NMR (376 MHz, CDCl_3) δ -115.07 (m).

Isomer 2: (*R*)-6-allyl-3-((*S*)-1-(4-bromophenyl)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one. LC-MS Method 1 $t_R = 1.98$ min, m/z 420, 418 (MH^+); ^1H NMR (400 MHz, CDCl_3) δ 7.25-7.20 (m, 4H), 7.05-7.01 (m, 2H), 6.71 (d, $J = 8.5$ Hz, 2H), 5.74-5.64 (m, 1H), 5.58 (q, $J = 7.0$ Hz, 1H), 5.09-4.99 (m, 2H), 2.92-2.87 (m, 1H), 2.63-2.50 (m, 2H), 2.33-2.16 (m, 3H), 1.47 (d, $J = 7.0$ Hz, 3H); ^{19}F NMR (376 MHz, CDCl_3) δ -114.91 (m).

Step 3

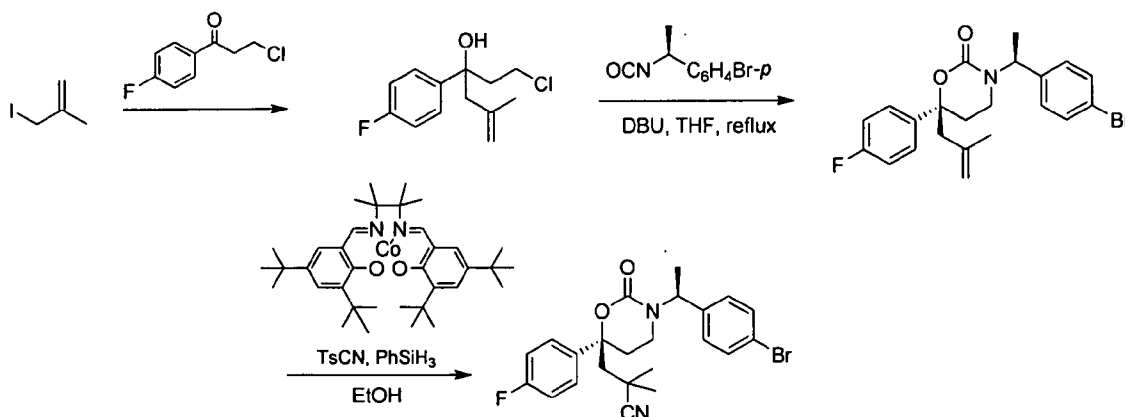
A mixture of (*R*)-6-allyl-3-((*S*)-1-(4-bromophenyl)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one (1.067 g, 2.55 mmol, 1.0 equiv), the cobalt(II) catalyst described in Preparation 3 (0.016 g, 0.0264 mmol, 0.010 equiv), TsCN (0.555 g, 3.06 mmol, 1.2 equiv), and PhSiH_3 (0.294 g, 2.72 mmol, 1.07 equiv) in EtOH (5 mL) was stirred at room temperature for 4 h. After the solvent was removed under reduced pressure, the residue was purified by chromatography on silica gel eluted with hexanes/ethyl acetate to afford 1.0130 g (89%) of 3-((*R*)-3-((*S*)-1-(4-bromophenyl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)-2-methylpropanenitrile as a solid. LC-MS $t_R = 1.83, 1.86$ min in 3 min chromatography, m/z 445, 447 (MH^+); ^1H NMR (400 MHz, CDCl_3) δ 7.32-7.22 (m, 4H), 7.13-7.05 (m, 2H), 6.80-6.73 (m, 2H), 5.60-5.56 (m, 1H), 3.00-1.94

(m, 7H), 1.51-1.49 (m, 3H), 1.35-1.32 (m, 1.5H), 1.27-1.24 (m, 1.5H); ^{19}F NMR (376 MHz, CDCl_3) δ -113.08 (m), -113.69(m).

Step 4

- 5 To a solution of 3-((*R*)-3-((*S*)-1-(4-bromophenyl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)-2-methylpropanenitrile (0.332 g, 0.746 mmol) and MeI (1.40 g, 13 equiv) in THF (12 mL) at -78°C was added 2.4 mL (2.4 mmol, 3.2 equiv) of a 1.0 M LiHMDS solution in THF. The resulting mixture was stirred overnight, with the temperature slowly rising to ambient. The reaction mixture was quenched with brine (1 mL), diluted with CH_2Cl_2 , and dried over Na_2SO_4 .
- 10 After the solvents were evaporated, the residue was purified by reversed-phase HPLC (SunFireTM Prep C_{18} OBDTM 5 μm 19 $\times$ 50 mm column, 10% $\rightarrow$ 90% $\text{CH}_3\text{CN}/\text{H}_2\text{O}$, 0.1% CF_3COOH over 8 min and then 90% $\text{CH}_3\text{CN}/\text{H}_2\text{O}$, 0.1% CF_3COOH over 2 min, flow rate 20 mL/min) to afford 0.255 g (74%) of 3-((*R*)-3-((*S*)-1-(4-bromophenyl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)-2,2-dimethylpropanenitrile. LC-MS Method 1 t_R = 1.89 min, m/z 459, 461 (MH^+); ^1H NMR (400 MHz, CD_3OD) δ 7.31-7.27 (m, 2H), 7.22-7.18 (m, 2H), 7.04-6.99 (m, 2H), 6.83 (d, J = 8.2 Hz, 2H), 5.41 (q, J = 7.0 Hz, 1H), 3.02-2.97 (m, 1H), 2.42-2.36 (m, 1H), 2.29-2.08 (m, 4H), 1.42 (d, J = 7.0 Hz, 3H), 1.30 (s, 3H), 1.22 (s, 3H); ^{19}F NMR (376 MHz, CD_3OD) δ -116.50 (m).
- 15

Method 2



Step 1

- A solution of 3-chloro-1-(4-fluorophenyl)propan-1-one (18.6 g, 0.1 mol) in THF (50 mL) was added to a well-stirred suspension of zinc powder (13 g, 0.2 mol) in a mixture of aqueous saturated NH_4Cl solution (260 mL) and THF (65 mL). A solution of 3-iodo-2-methylprop-1-ene (36.4 g, 0.2 mol) in THF (50 mL) was added dropwise. The reaction mixture was mildly exothermic, and began to reflux spontaneously. After the refluxing had ceased, the mixture was stirred for 1 h. TLC showed the 3-chloro-1-(4-fluorophenyl)propan-1-one not reacted completely. A solution of 3-iodo-2-methylprop-1-ene (18.2 g, 0.1 mol) in THF (30 mL) was added, and the
- 25

mixture was stirred at rt overnight. The mixture was extracted with EtOAc (2 x 500 mL). The combined organic layer was dried and concentrated. The residue was purified by column chromatography on silica gel eluted with petroleum ether/ EtOAc 50:1→30:1→5:1, to give 1-chloro-3-(4-fluorophenyl)-5-methylhex-5-en-3-ol (17 g, yield 76 %) as an oil.

5

Step 2

A mixture of 1-chloro-3-(4-fluorophenyl)-5-methylhex-5-en-3-ol (3.15 g, 13 mmol), (S)-(-)-1-(4-bromophenyl)ethyl isocyanate (3.5 g, 16 mmol), and DBU (8 g, 33 mmol) in THF (80 mL) was heated to reflux for 25 h. The mixture was diluted with EtOAc and washed with 1N aq HCl. The aqueous phase was extracted with EtOAc (3 x). The combined organic phase was dried over Na₂SO₄. After the solvents were evaporated, the crude product was purified by column to give (R)-3-((S)-1-(4-bromophenyl)ethyl)-6-(4-fluorophenyl)-6-(2-methylallyl)-1,3-oxazinan-2-one (2.13 g, yield: 38 %).

10

Step 3

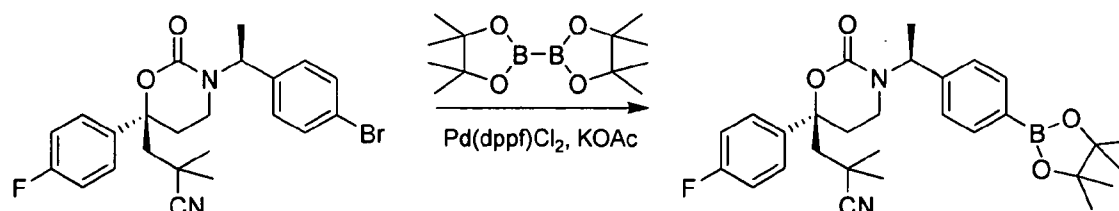
A mixture of (R)-3-((S)-1-(4-bromophenyl)ethyl)-6-(4-fluorophenyl)-6-(2-methylallyl)-1,3-oxazinan-2-one (2.13 g, 4.9 mmol), the cobalt(II) catalyst described in Preparation 3 (0.032 g, 0.053 mmol), TsCN (1.11 g, 6.12 mmol), and PhSiH₃ (0.6 g, 5.54 mmol) in EtOH (10 mL) was stirred at room temperature for 8 h. After the solvent was removed under reduced pressure, the residue was purified by column chromatography to give 3-((R)-3-((S)-1-(4-bromophenyl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)-2,2-dimethylpropanenitrile (1.84 g, 81.1 %).

20

PREPARATION 6

3-((R)-3-((S)-1-(4-bromophenyl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)-2,2-dimethylpropanenitrile

25



To a solution of 3-((R)-3-((S)-1-(4-bromophenyl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)-2,2-dimethylpropanenitrile (730 mg, 1.59 mmol) in DMSO (8 mL) was added bis(pinacolato)diboron (480 mg, 1.89 mmol), KOAc (480 mg, 4.89 mmol) and Pd(dppf)Cl₂ (45 mg, 0.042 mmol) under nitrogen atmosphere. The formed mixture was stirred at 90 °C for 20 h. The reaction was quenched with water and extracted with EtOAc. The combined organic phase was dried over anhydrous Na₂SO₄ and concentrated to give the crude product, which was purified by

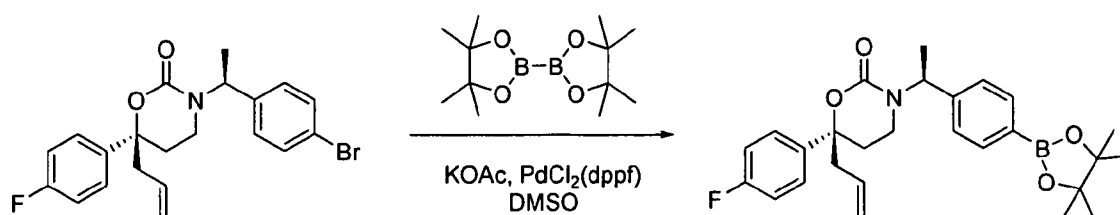
30

column chromatography to give 3-((*R*)-6-(4-fluorophenyl)-2-oxo-3-((*S*)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl)-1,3-oxazinan-6-yl)-2,2-dimethylpropanenitrile (191 mg, 23.7%).

5

PREPARATION 7

(*R*)-6-allyl-6-(4-fluorophenyl)-3-((*S*)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl)-1,3-oxazinan-2-one

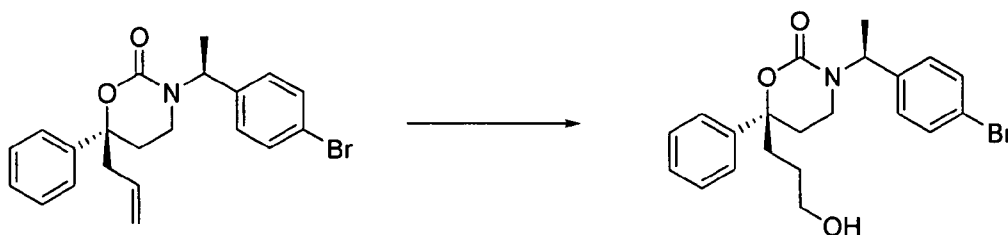


A mixture of (*R*)-6-allyl-3-((*S*)-1-(4-bromophenyl)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one (0.4910 g, 1.17 mmol, 1.0 equiv), bis(pinacolato)diboron (0.3925 g, 1.55 mmol, 1.3 equiv), KOAc (0.3696 g, 3.76 mmol, 3.2 equiv), and PdCl₂(dppf)·CH₂Cl₂ (0.0316 g, 0.0386 mmol, 0.033 equiv) in DMSO (6 mL) was heated at 90 °C under N₂ for 20 h. After cooling, the reaction mixture was partitioned between EtOAc and water. The organic phase was washed with brine, and dried over Na₂SO₄. After the solvents were evaporated, the residue was purified by chromatography on silica gel eluted with hexanes/ethyl acetate to give 0.4776 g (87%) of (*R*)-6-allyl-6-(4-fluorophenyl)-3-((*S*)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl)-1,3-oxazinan-2-one as a white solid.

20

PREPARATION 8

(*R*)-3-((*S*)-1-(4-bromophenyl)ethyl)-6-(3-hydroxypropyl)-6-phenyl-1,3-oxazinan-2-one



To a solution of (*R*)-6-allyl-3-((*S*)-1-(4-bromophenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one (5 g, 12.5 mmol) in tetrahydrofuran (60 mL) was added BH₃·THF (25 mL, 1 mol/L, 25 mmol) at 0 °C under nitrogen atmosphere. The formed mixture was stirred for 2 h. The reaction was quenched with water. Then NaOH (3 mol/L, 10 mL) and H₂O₂ (15 mL) were added to the above mixture. When the reaction was over, the mixture was extracted with EtOAc. The combined

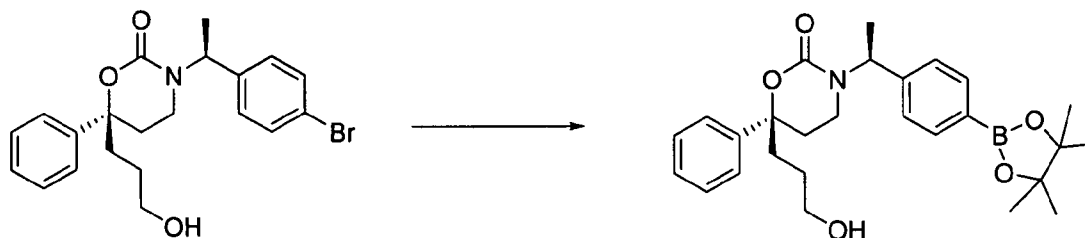
organic phase was concentrated to give the crude product, which was purified by column chromatography to give (*R*)-3-((*S*)-1-(4-bromophenyl)ethyl)-6-(3-hydroxypropyl)-6-phenyl-1,3-oxazinan-2-one (2.5 g, 40%). ¹H NMR: (400MHz, CDCl₃): δ=1.48 (t, 3H), 1.53 (m, 1H), 1.73 (m, 1H), 1.93-1.98(m, 2H), 2.17-2.28 (m,3H), 3.57 (t, 2H), 5.59 (m, 1H), 6.72 (m, 2H), 7.20(m, 2H), 7.25-7.37 (m, 5H).

(*R*)-3-((*S*)-1-(4-bromophenyl)ethyl)-6-(4-fluorophenyl)-6-(3-hydroxypropyl)-1,3-oxazinan-2-one was prepared from (*R*)-6-allyl-3-((*S*)-1-(4-bromophenyl)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one following an analogous procedure.

(*R*)-3-((*S*)-1-(4-bromophenyl)propyl)-6-(3-hydroxypropyl)-6-phenyl-1,3-oxazinan-2-one was prepared from (*R*)-6-allyl-3-((*S*)-1-(4-bromophenyl)propyl)-6-phenyl-1,3-oxazinan-2-one following an analogous procedure.

PREPARATION 9

(*R*)-6-(3-hydroxypropyl)-6-phenyl-3-((*S*)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl)-1,3-oxazinan-2-one



To a solution of ((*R*)-3-((*S*)-1-(4-bromophenyl)ethyl)-6-(3-hydroxypropyl)-6-phenyl-1,3-oxazinan-2-one (2 g, 4.8 mmol) in DMSO (30 mL) were added bis(pinacolato)diboron (1.58 g, 6.3 mmol), KOAc (1.51 g, 15.4 mmol) and PdCl₂ (130 mg, 0.16 mmol) under nitrogen atmosphere. The formed mixture was stirred at 90 °C for 20 h. The reaction was quenched with water and extracted with EtOAc. The combined organic phase was concentrated to give the crude product, which was purified by column chromatography to give (*R*)-6-(3-hydroxypropyl)-6-phenyl-3-((*S*)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl)-1,3-oxazinan-2-one (1.7 g, 77%). ¹H NMR: (400MHz, CDCl₃): δ=1.18 (t, 1H), 1.33 (s, 11H), 1.43 (m, 2H), 1.48 (m, 3H), 1.71(m, 1H), 1.88 (m,2H), 2.1-2.3 (t, 3H), 2.7(m, 1H) , 3.5 (m, 2H), 5.5 (m, 1H), 6.72 (m, 2H), 7.25-7.37 (m, 5H), 7.48(m, 2H).

(R)-6-(4-fluorophenyl)-6-(3-hydroxypropyl)-3-((S)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl)-1,3-oxazinan-2-one was prepared from (R)-3-((S)-1-(4-bromophenyl)ethyl)-6-(4-fluorophenyl)-6-(3-hydroxypropyl)-1,3-oxazinan-2-one following an analogous procedure.

5

(R)-6-(3-hydroxypropyl)-6-phenyl-3-((S)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propyl)-1,3-oxazinan-2-one was prepared from (R)-3-((S)-1-(4-bromophenyl)propyl)-6-(3-hydroxypropyl)-6-phenyl-1,3-oxazinan-2-one following an analogous procedure.

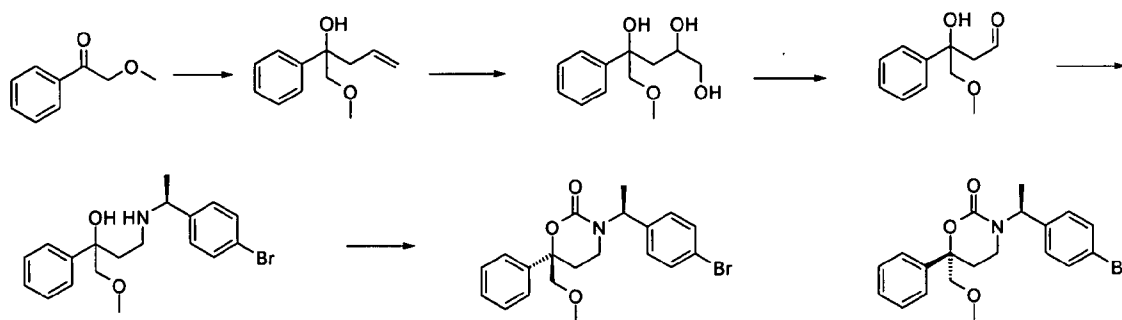
10

(R)-6-(3-hydroxypropyl)-6-phenyl-3-((S)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propyl)-1,3-oxazinan-2-one was prepared from (R)-3-((S)-1-(4-bromophenyl)propyl)-6-(3-hydroxypropyl)-6-phenyl-1,3-oxazinan-2-one following an analogous procedure.

PREPARATION 10

15

(R)-3-((S)-1-(4-bromophenyl)ethyl)-6-(methoxymethyl)-6-phenyl-1,3-oxazinan-2-one



Step 1. 1-Methoxy-2-phenyl-pent-4-en-2-ol

2-Methoxy-1-phenyl-ethanone (5.00 g) dissolved in tetrahydrofuran (50 mL) was added to 2 M allylmagnesium chloride in tetrahydrofuran (21 mL) at room temperature. The solution was stirred at room temperature for 3 h and then 10 % aqueous NH_4Cl solution (50 mL) was added. The resulting mixture was extracted with tert-butyl methyl ether (3x 50 mL) and the combined extracts were washed with water (50 mL) and brine (50 mL). The solvent was evaporated to afford the title compound as a colorless oil.

Yield: 6.40 g (quantitative). Mass spectrum (ESI^+): $m/z = 175$ [$\text{M}+\text{H}-\text{H}_2\text{O}$] $^+$

Step 2. 5-Methoxy-4-phenyl-pentane-1,2,4-triol

OsO_4 (4% in water, 2 mL; alternatively, K_2OsO_4 may be used) followed by N-methyl-morpholine-N-oxide (5.20 g) was added to a solution of 1-methoxy-2-phenyl-

pent-4-en-2-ol (1.10 g) in tetrahydrofuran (10 mL) chilled in an ice bath. The cooling bath was removed and the solution was stirred at room temperature overnight. Then, 10% aqueous Na₂S₂O₅ solution (10 mL) was added and the resulting mixture was stirred at room temperature for another 1.5 h. After removal of the organic solvent under reduced pressure, the remaining mixture was extracted with ethyl acetate. The combined extracts were washed with brine and dried (MgSO₄). The solvent was evaporated to afford the title compound in good purity (ca. 95%). Yield: 1.20 g (96% of theory). Mass spectrum (ESI): m/z = 225 [M-H]⁻

10 Step 3. 3-Hydroxy-4-methoxy-3-phenyl-butyraldehyde

NaIO₄ (5.20 g) was added to a mixture of 5-methoxy-4-phenyl-pentane-1,2,4-triol (1.10 g), dichloromethane (10 mL), and water (5 mL) chilled in an ice bath. The mixture was stirred vigorously while warming to ambient temperature in the cooling bath and further stirred at this temperature overnight. Then, water (20 mL) and dichloromethane (50 mL) were added, the organic layer was separated, and the aqueous layer was extracted with dichloromethane (2x 25 mL). The combined organic phases were washed with water and dried (MgSO₄). After removal of the solvent, the title compound was yielded which was directly submitted to the next reaction step (glycol cleavage). Yield: 0.94 g (quantitative)

20

Step 4. 4-[(S)-1-(4-Bromo-phenyl)-ethylamino]-1-methoxy-2-phenyl-butan-2-ol

(S)-1-(4-Bromo-phenyl)-ethylamine (0.93 g), NaB(OAc)₃ (0.98 g), and acetic acid (0.27 mL) were added in the given order to a solution of 3-hydroxy-4-methoxy-3-phenyl-butyraldehyde (0.90 g) in tetrahydrofuran (20 mL) at ca. 10-15 °C. The cooling bath was removed and the mixture was stirred at room temperature for 2 h. Then, water (50 mL) and 1 M aqueous NaOH solution (20 mL) were added and the resulting mixture was stirred for another 30 min. The mixture was extracted with ethyl acetate and the combined extracts were washed with water and brine. After drying (MgSO₄), the solvent was removed to give the title compound which was submitted to the subsequent reaction step without further purification. Yield: 1.80 g (quantitative). Mass spectrum (ESI⁺): m/z = 378/380 (Br) [M+H]⁺

30

Step 5. 3-[(S)-1-(4-Bromo-phenyl)-ethyl]-(R)-6-methoxymethyl-6-phenyl-[1,3]oxazinan-2-one and 3-[(S)-1-(4-Bromo-phenyl)-ethyl]-(S)-6-methoxymethyl-6-phenyl-[1,3]oxazinan-2-one

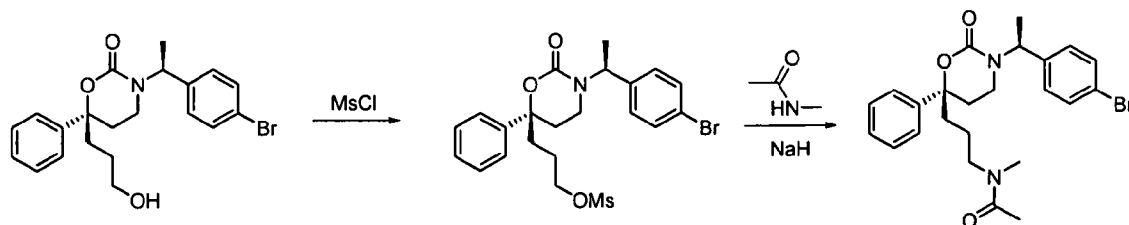
Triphosgene (157 mg) was added to an ice-cold solution of 4-[(*S*)-1-(4-bromo-phenyl)-ethylamino]-1-methoxy-2-phenyl-butan-2-ol (1:1 diastereomeric mixture, 200 mg) and Et₃N/Pr₂ (91 μ L) in dichloromethane (5 mL). The resulting solution was stirred with cooling for 2 h and at room temperature overnight. Then, the solution was concentrated under reduced pressure and the residue was purified by HPLC on reversed phase (MeCN/H₂O/NH₃) to afford the title compounds in separate fractions.

Isomer 1: 3-[(*S*)-1-(4-Bromo-phenyl)-ethyl]-(*R*)-6-methoxymethyl-6-phenyl-[1,3]oxazinan-2-one. Yield: 45 mg (21% of theory). Mass spectrum (ESI⁺): *m/z* = 404 [M+H]⁺ ¹H NMR (400 MHz, DMSO-*d*₆) δ 1.41 (d, *J* = 7.1 Hz, 3H), 2.19 (td, *J* = 11.2, 5.2 Hz, 1H), 2.24-2.34 (m, 1H), 2.34-2.41 (m, 1H), 3.02-3.09 (m, 1H), 3.27 (s, 3H), 3.49 (d, B part of an AB signal, *J* = 10.6 Hz, 1H), 3.53 (d, A part of an AB signal, *J* = 10.6 Hz, 1H), 5.34 (q, *J* = 7.0 Hz, 1H), 6.80 (dm, *J* = 8.4 Hz, 2H), 7.27 (dm, *J* = 8.4 Hz, 2H), 7.32-7.42 (m, 5H).

Isomer 2: 3-[(*S*)-1-(4-Bromo-phenyl)-ethyl]-(*S*)-6-methoxymethyl-6-phenyl-[1,3]oxazinan-2-one. Yield: 45 mg (21% of theory). Mass spectrum (ESI⁺): *m/z* = 404 [M+H]⁺ ¹H NMR (400 MHz, DMSO-*d*₆) δ 1.20 (d, *J* = 7.2 Hz, 3H), 2.13-2.23 (m, 1H), 2.32-2.40 (m, 1H), 2.63-2.72 (m, 1H), 2.73-2.81 (m, 1H), 3.26 (s, 3H), 3.48 (d, B part of an AB signal, *J* = 10.6 Hz, 1H), 3.55 (d, A part of an AB signal, *J* = 10.6 Hz, 1H), 5.35 (q, *J* = 7.2 Hz, 1H), 7.19 (dm, *J* = 8.4 Hz, 2H), 7.32-7.45 (m, 5H), 7.53 (dm, *J* = 8.4 Hz, 2H).

PREPARATION 11

N-(3-((*R*)-3-((*S*)-1-(4-bromophenyl)ethyl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)propyl)-N-methylacetamide



Step 1

To a solution of (*R*)-3-((*S*)-1-(4-bromophenyl)ethyl)-6-(3-hydroxypropyl)-6-phenyl-1,3-oxazinan-2-one (200 mg, 0.48 mmol) in CH₂Cl₂ (5 mL) was added Et₃N (240 mg, 2.4 mmol) and methanesulfonyl chloride (164 mg, 1.4 mmol) at 0 °C. The reaction solution was stirred at rt for 1 h. The reaction was quenched with H₂O and the mixture was extracted with CH₂Cl₂. The organic

phase was concentrated to give 3-((*R*)-3-((*S*)-1-(4-bromophenyl)ethyl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)propyl methanesulfonate (234 mg, 98%), which was used for the next step without further purification.

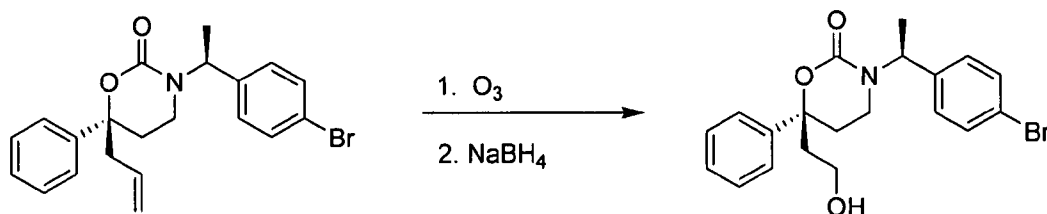
5 Step 2

To a solution of 3-((*R*)-3-((*S*)-1-(4-bromophenyl)ethyl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)propyl methanesulfonate (234 mg, 0.24 mmol) in CH_2Cl_2 (3 mL) was added NaH (82 mg, 3.4 mmol) at 0 °C. The mixture was stirred at rt for 30 min. Then *N*-methylacetamide (204 mg, 2.8 mmol) was added the above mixture. The formed mixture was stirred at 80 °C for 5 h. After the reaction was over, the reaction was quenched with water and the mixture was extracted with EtOAc. The combined organic phase was concentrated to give the crude product, which was purified by preparative TLC to give *N*-(3-((*R*)-3-((*S*)-1-(4-bromophenyl)ethyl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)propyl)-*N*-methylacetamide (150 mg, 68%). LC-MS Method 2 tR = 1.50 min, m/z = 497, 495, 475, 473. ^1H NMR (400MHz, CDCl_3): δ =1.41 (m, 1H), 1.48 (t, 3H), 1.73 (m, 1H), 1.83-1.95 (m, 2H), 2.01 (m, 3H), 2.1-2.3 (m, 3H), 2.71 (m, 1H), 2.81 (s, 3H), 3.1 (m, 1H), 3.2 (m, 1H), 5.5 (m, 1H), 6.72 (m, 2H), 7.10 (m, 2H), 7.20 (m, 2H), 7.37 (m, 3H).

(*R*)-3-((*S*)-1-(4-bromophenyl)ethyl)-6-(3-(2-oxopyrrolidin-1-yl)propyl)-6-phenyl-1,3-oxazinan-2-one was prepared from (*R*)-3-((*S*)-1-(4-bromophenyl)ethyl)-6-(3-hydroxypropyl)-6-phenyl-1,3-oxazinan-2-one following an analogous procedure using pyrrolidin-2-one in Step 2.

PREPARATION 12

(*S*)-3-((*S*)-1-(4-bromophenyl)ethyl)-6-(2-(1,1-dioxo-isothiazolidin-2-yl)ethyl)-6-phenyl-1,3-oxazinan-2-one



To a solution of (*R*)-6-allyl-3-((*S*)-1-(4-bromophenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one (3 g, 7.5 mmol) in CH_2Cl_2 (50 mL) was treated with O_3 at -78 °C till the mixture turned blue. Then NaBH_4 (285 mg, 75 mmol) was added to the solution at 0 °C, and the reaction solution was stirred at room temperature for 3 hours. The reaction was quenched by H_2O , and the mixture was extracted with EtOAc. The combined organic phase was concentrated to give the crude product,

which was purified by preparative TLC to give (S)-3-((S)-1-(4-bromophenyl)ethyl)-6-(2-hydroxyethyl)-6-phenyl-1,3-oxazinan-2-one (2.5 g, 84%). ¹H NMR (CDCl₃): 1.48 (t, 3H), 2.05-2.41 (m, 4H), 2.71-2.92 (m, 2H), 3.51 (m, 1H), 3.71 (m, 1H), 5.58 (m, 1H), 6.73 (d, 2H), 7.12 (m, 2H), 7.23-7.45 (m, 6H).

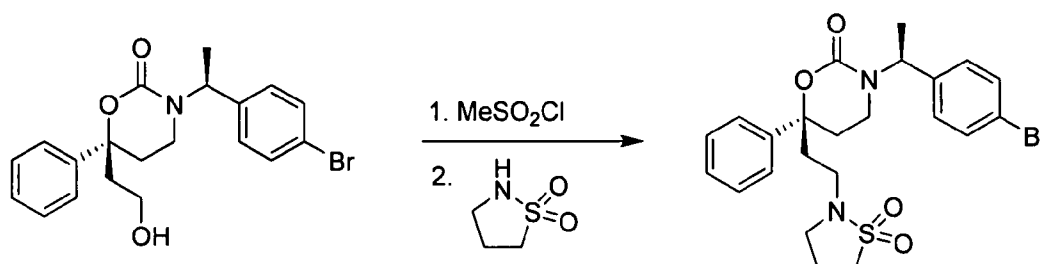
5

(S)-3-((S)-1-(4-bromophenyl)propyl)-6-(2-hydroxyethyl)-6-phenyl-1,3-oxazinan-2-one was prepared from (R)-6-allyl-3-((S)-1-(4-bromophenyl)propyl)-6-phenyl-1,3-oxazinan-2-one following a procedure analogous to that described immediately above.

10

PREPARATION 13

(S)-3-((S)-1-(4-bromophenyl)ethyl)-6-(2-(1,1-dioxo-isothiazolidin-2-yl)ethyl)-6-phenyl-1,3-oxazinan-2-one



Step 1

15

To a solution of (S)-3-((S)-1-(4-bromophenyl)ethyl)-6-(2-hydroxyethyl)-6-phenyl-1,3-oxazinan-2-one (300 mg, 0.75 mmol) in dichloromethane (20 mL) were added Et₃N (390 mg, 3.75 mmol) and methanesulfonyl chloride (256 mg, 2.25 mmol) at 0 °C. The reaction solution was stirred at rt for 1 h. The reaction was quenched with H₂O and the mixture was extracted with dichloromethane. The organic phase was concentrated to give 2-((S)-3-((S)-1-(4-bromophenyl)ethyl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)ethyl-methane sulfonate (352.8 mg, 98%), which was used for the next step without further purification.

20

Step 2

To a solution of 2-((S)-3-((S)-1-(4-bromophenyl)ethyl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)ethyl-methanesulfonate (360 mg, 0.75 mmol) and K₂CO₃ (207 mg, 1.5 mmol) in acetonitrile (10 mL) was added isothiazolidine 1,1-dioxide (121 mg, 4.6 mmol), and the mixture was refluxed overnight. The mixture was filtered and the filtrate was concentrated to give the crude product, which was purified by preparative HPLC to afford compound (S)-3-((S)-1-(4-bromophenyl)ethyl)-6-(2-(1,1-dioxo-isothiazolidin-2-yl)ethyl)-6-phenyl-1,3-oxazinan-2-one (2.43 mg, 1%). LC-MS Method 2 t_R = 1.37 min, m/z = 509, 507. ¹H NMR (CDCl₃): 1.48 (t, 3H), 2.05-2.41 (m, 7H), 2.71-

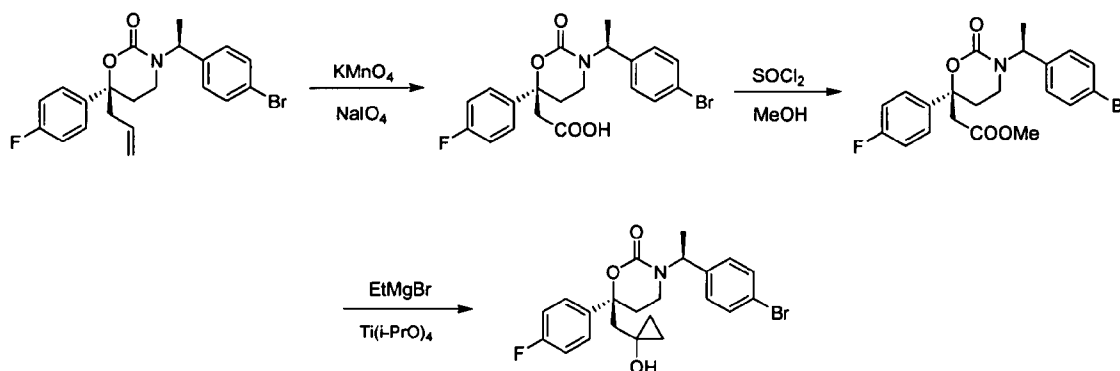
30

2.92 (m, 2H), 3.11 (m, 3H), 3.21 (m, 2H), 5.58 (m, 1H), 6.73 (d, 2H), 7.18 (m, 1H), 7.23 (m, 3H); 7.35 (m, 3H).

(R)-3-((S)-1-(4-bromophenyl)ethyl)-6-(3-(1,1-dioxo-isothiazolidin-2-yl)propyl)-6-phenyl-1,3-oxazinan-2-one was prepared from from from (R)-3-((S)-1-(4-bromophenyl)ethyl)-6-(3-hydroxypropyl)-6-phenyl-1,3-oxazinan-2-one following an analogous procedure.

PREPARATION 14

(S)-3-((S)-1-(4-bromophenyl)ethyl)-6-(4-fluorophenyl)-6-((1-hydroxycyclopropyl)methyl)-1,3-oxazinan-2-one



Step 1

To a solution of (R)-6-allyl-3-((S)-1-(4-bromophenyl)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one (450 mg, 1.01 mmol) in acetone (10 mL) was added a solution of KMnO_4 (190 mg, 1.2 mmol) and NaIO_4 (1.5 g, 7.2 mmol) in water (10 mL). The mixture was stirred for 2 h at 0 °C. The mixture was filtered and the filtrate was adjusted to pH 5-6 with aqueous 1 N aq HCl solution. The mixture was extracted with EtOAc. The organic phase washed with brine, dried over anhydrous Na_2SO_4 and concentrated to give 2-((S)-3-((S)-1-(4-bromophenyl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)acetic acid (540 mg, crude), which was used for the next step without purification.

Step 2

To a solution of 2-((S)-3-((S)-1-(4-bromophenyl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)acetic acid (540 mg, 1.24 mol) in MeOH (20 mL) was added SOCl_2 (5 mL) at 0 °C, and the reaction mixture was stirred at rt for 2 h. The reaction mixture was concentrated and the residue was purified by preparative TLC to give methyl 2-((S)-6-(4-fluorophenyl)-3-((S)-1-(4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-ethyl)-2-oxo-1,3-oxazinan-6-yl)acetate (150 mg,

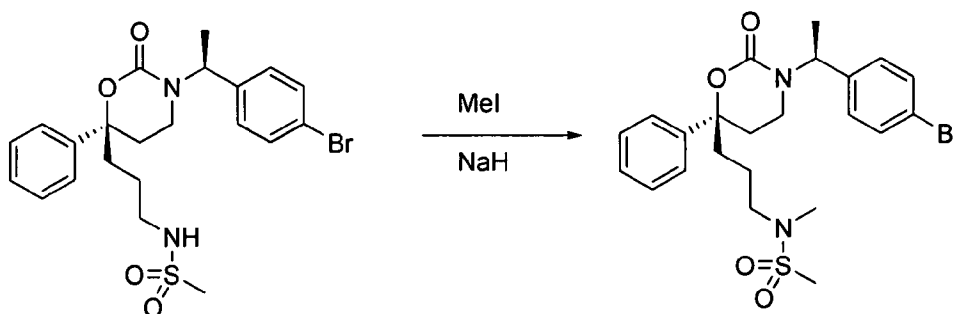
27%). ^1H NMR (CDCl_3): δ =1.49 (d, 3H), 2.19 (m, 1H), 2.44 (m, 1H), 2.60 (m, 1H), 2.77-3.08 (m, 3H), 3.51 (s, 3H), 5.52 (m, 2H), 6.62 (d, 2H), 6.98 (t, 2H), 7.23 (t, 2H), 7.28 (m, 2H).

Step 3

- 5 To a solution of methyl 2-((S)-6-(4-fluorophenyl)-3-((S)-1-(4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)-ethyl)-2-oxo-1,3-oxazinan-6-yl)acetate (150 mg, 0.33 mmol), and tetraisopropoxytitanium (189 mg, 0.66 mmol) in THF (20 mL) was added 3.0 M ethylmagnesium bromide (4 mL, 12 mmol) at rt under nitrogen. Then the mixture was stirred for 2 h. The reaction was quenched with aqueous NH_4Cl solution, and the mixture was filtered. The filtrate was
- 10 extracted with EtOAc. The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4 , and concentrated to give the crude product, which was purified by preparative HPLC to give (S)-3-((S)-1-(4-bromophenyl)ethyl)-6-(4-fluorophenyl)-6-((1-hydroxycyclopropyl)methyl)-1,3-oxazinan-2-one (2.51 mg, 2%). ^1H NMR (CDCl_3): 0.03 (m, 1H), 0.18 (m, 1H), 0.49 (m, 1H), 0.60 (m, 1H), 1.43 (m, 3H), 2.08 (s, 2H), 2.26 (m, 1H), 2.37 (m, 2H),
- 15 2.88 (m, 1H), 5.53 (m, 1H), 6.66 (d, 2H), 6.97 (t, 2H), 7.16 (m, 2H), 7.26 (m, 2H).

PREPARATION 15

N-(3-((R)-3-((S)-1-(4-bromophenyl)ethyl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)propyl)-N-methylmethanesulfonamide



20

- To a solution of 3-((R)-3-((S)-1-(4-bromophenyl)ethyl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)propyl methanesulfonate (180 mg, 0.36 mmol) in DMF (5 mL) was added NaH (14.6 mg, 0.36 mmol) at 0 °C. The mixture was stirred at rt for 30 min. Then iodomethane (153 mg, 1.1 mmol)
- 25 was added to the above mixture. The formed mixture was stirred at 40 °C for 3 h. After the reaction was over, the reaction was quenched with NH_4Cl solution and the mixture was extracted with EtOAc. The combined organic phase was concentrated to give the crude product, which was purified by preparative TLC to give N-(3-((R)-3-((S)-1-(4-bromophenyl)ethyl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)propyl)-N-methylmethanesulfonamide (100 mg, 55%). LC-MS Method 2 t_R =
- 30 1.41 min, m/z = 511, 509. ^1H NMR (400MHz, CDCl_3): δ =1.45 (m, 1H), 1.48 (t, 3H), 1.83-1.97 (m,

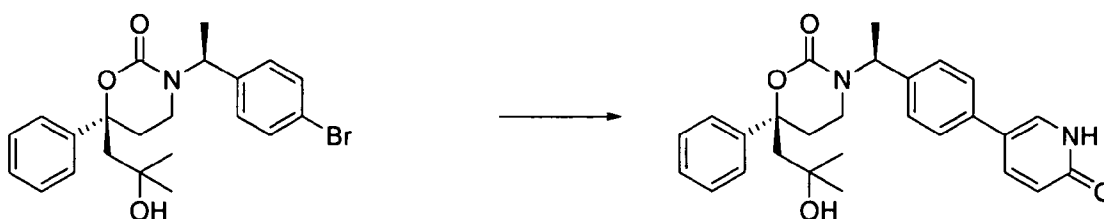
3H), 2.1-2.2 (m, 3H), 2.61 (s, 3H), 2.71 (s, 3H), 2.91 (m, 1H), 3.0 (m, 2H), 5.5 (m, 1H), 6.72 (m, 2H), 7.10 (m, 2H), 7.20 (m, 2H), 7.37 (m, 3H).

5

EXAMPLE 1

(S)-6-(2-hydroxy-2-methylpropyl)-3-((S)-1-(4-(6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one

10



15

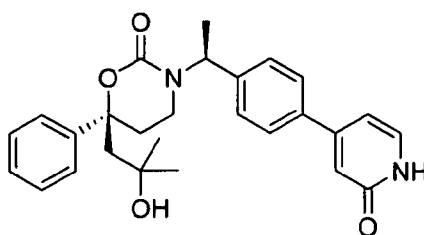
To a solution of (S)-3-((S)-1-(4-bromophenyl)ethyl)-6-(2-hydroxy-2-methylpropyl)-6-phenyl-1,3-oxazinan-2-one (112 mg, 0.259 mmol) in 1,4-dioxane (3 mL) was added 6-oxo-1,6-dihydropyridin-3-ylboronic acid (55 mg, 0.40 mmol), followed by Pd(dppf)Cl₂ (11 mg, 0.015 mmol), and an aq solution of Cs₂CO₃ (0.48 mL, 2M in H₂O). A reflux condenser was attached and the apparatus was degassed and flushed with N₂ three times. The reaction was heated to 90 °C for 24 h. After cooling to rt the mixture was diluted with water and extracted three times with EtOAc. The organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated. The residue was purified by prep HPLC to afford the title compounds (21.6 mg) as an oil. LC-MS Method 1 t_R = 1.25 min, m/z = 447, 389; ¹H NMR (CD₃OD) 0.96 (s, 3H), 1.28 (s, 3H), 1.57 (d, 3H), 2.16 (s, 2H), 2.21 (m, 1H), 2.46 (m, 2H), 3.03 (m, 1H), 5.57 (q, 1H), 6.66 (d, 1H), 7.02 (d, 2H), 7.25-7.40 (7H), 7.66 (s, 1H), 7.90 (d, 1H).

20

EXAMPLE 2

25

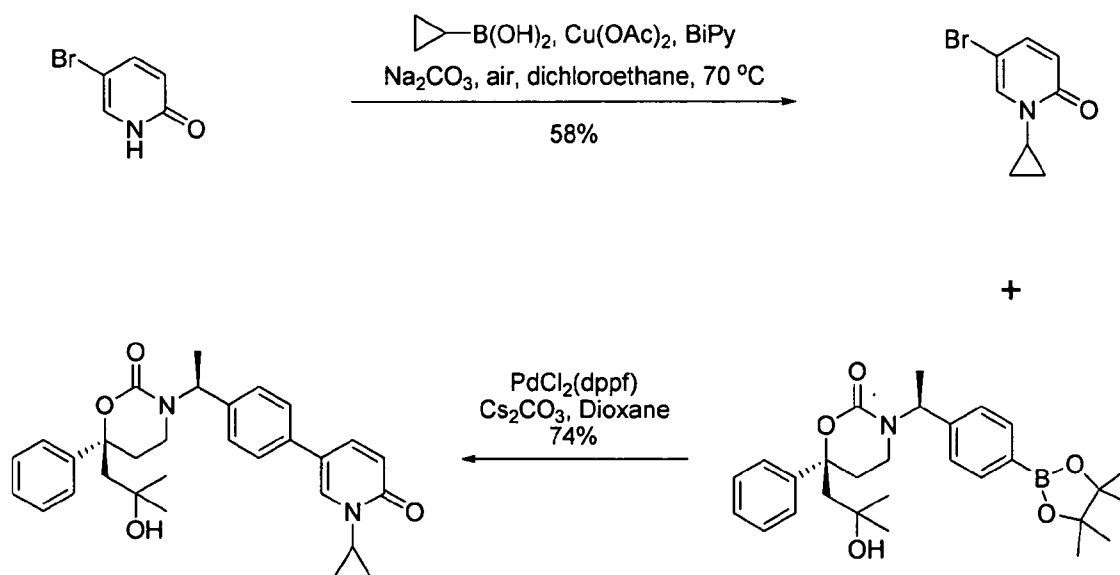
(S)-6-(2-hydroxy-2-methylpropyl)-3-((S)-1-(4-(2-oxo-1,2-dihydropyridin-4-yl)phenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one



The title compound was prepared from (S)-6-(2-hydroxy-2-methylpropyl)-6-phenyl-3-((S)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl)-1,3-oxazinan-2-one and 4-iodopyridin-2(1H)-one following a procedure analogous to that described in Example 1. LC-MS Method 1 t_R = 1.23 min, m/z = 389, 447 ($M+1$); ^1H NMR (CD_3OD) 7.40 (d, J = 6.7 Hz, 1H), 7.31 (d, J = 8.2 Hz, 2H), 7.29-7.20 (m, 5H), 6.96 (d, J = 8.2 Hz, 2H), 6.57-6.52 (m, 2H), 5.49 (q, J = 7.0 Hz, 1H), 2.98-2.93 (m, 1H), 2.47-2.34 (m, 2H), 2.16-2.09 (m, 1H), 2.07 (s, 2H), 1.45 (d, J = 7.0 Hz, 3H), 1.19 (s, 3H), 0.87 (s, 3H).

EXAMPLE 3

(S)-3-((S)-1-(4-(1-cyclopropyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-6-(2-hydroxy-2-methylpropyl)-6-phenyl-1,3-oxazinan-2-one



Step 1. 5-bromo-1-cyclopropylpyridin-2(1H)-one

A mixture of 5-bromo-2-hydroxypyridine (0.8300 g, 4.77 mmol, 1.0 equiv), $Cu(OAc)_2$ (0.902 g, 4.96 mmol, 1.04 equiv), bipyridine (0.785 g, 5.03 mmol, 1.05 equiv), cyclopropylboronic acid (0.846 g, 9.85 mmol, 2.06 equiv) and Na_2CO_3 (1.110 g, 10.47 mmol, 2.20 equiv) in dichloroethane (30 mL) was stirred at 70 °C for 22 h under air. The reaction mixture was quenched with satd aq NH_4Cl , diluted with CH_2Cl_2 , dried over Na_2SO_4 . After the solvent was removed under reduced pressure, the residue was purified by chromatography on silica gel eluted with hexanes/EtOAc to afford 0.585 g (58%) of 5-bromo-1-cyclopropylpyridin-2(1H)-one. LC-MS Method 1 t_R = 1.05 min, m/z 214, 216 (MH^+); ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, J = 2.7 Hz, 1H), 7.31 (dd, J = 9.7, 2.9 Hz, 1H), 6.47 (d, J = 9.9 Hz, 1H), 3.33-3.27 (m, 1H), 1.17-1.12 (m,

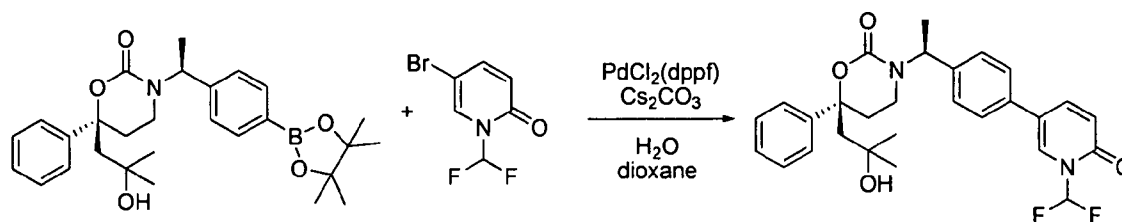
2H), 0.89-0.84 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 162.58, 142.29, 137.00, 121.77, 97.92, 32.83, 6.93.

Step 2. (S)-3-((S)-1-(4-(1-cyclopropyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-6-(2-hydroxy-2-methylpropyl)-6-phenyl-1,3-oxazinan-2-one

To a solution of (S)-6-(2-hydroxy-2-methylpropyl)-6-phenyl-3-((S)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl)-1,3-oxazinan-2-one (0.729 g, 1.52 mmol) in 1,4-dioxane (16 mL) were added 5-bromo-1-cyclopropylpyridin-2(1H)-one (0.323 g, 1.51 mmol), 2 M aq Cs_2CO_3 (4 mL), and $\text{PdCl}_2(\text{dppf})\cdot\text{CH}_2\text{Cl}_2$ (0.079 g, 0.0964 mmol). The mixture was degassed and heated, under a nitrogen atmosphere, at 120 °C for 16 h. The mixture was diluted with CH_2Cl_2 , dried over Na_2SO_4 . After the solvents were evaporated, the residue was purified by chromatography on silica gel eluted with $\text{MeOH}/\text{CH}_2\text{Cl}_2$ to afford 0.543 g (74%) of (S)-3-((S)-1-(4-(1-cyclopropyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-6-(2-hydroxy-2-methylpropyl)-6-phenyl-1,3-oxazinan-2-one. LC-MS Method 1 t_R = 1.41 min, m/z 487 (MH^+); ^1H NMR (400 MHz, CD_3OD) δ 7.66-7.64 (m, 2H), 7.30-7.19 (m, 7H), 6.94 (d, J = 8.2 Hz, 2H), 6.52 (d, J = 10 Hz, 1H), 5.48 (q, J = 7.0 Hz, 1H), 3.32-3.26 (m, 1H), 2.97-2.92 (m, 1H), 2.46-2.32 (m, 2H), 2.16-2.09 (m, 1H), 2.08 (s, 2H), 1.45 (d, J = 7.0 Hz, 3H), 1.19 (s, 3H), 1.10-1.05 (m, 2H), 0.90-0.86 (m, 5H); ^{13}C NMR (100 MHz, CD_3OD) δ 165.59, 155.82, 144.08, 141.05, 139.60, 136.60, 136.30, 129.77, 128.86, 128.64, 126.83, 126.15, 121.93, 120.53, 85.33, 71.67, 55.18, 54.78, 37.46, 34.10, 33.04, 31.79, 30.00, 15.60, 7.49, 7.47.

EXAMPLE 4

(S)-3-((S)-1-(4-(1-(difluoromethyl)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-6-(2-hydroxy-2-methylpropyl)-6-phenyl-1,3-oxazinan-2-one



A microwave vial equipped with a flea stirbar was charged with (S)-6-(2-hydroxy-2-methylpropyl)-6-phenyl-3-((S)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl)-1,3-oxazinan-2-one (20 mg, 0.047 mmol), 5-bromo-1-(difluoromethyl)pyridin-2(1H)-one (25 mg, 0.113 mmol), Cs_2CO_3 (27 mg, 0.083 mmol), H_2O (0.1 mL) and dry dioxane (1 mL). The mixture was sparged with N_2 for 10 min and heated at 110 °C in the microwave for 0.5 h. The mixture was diluted with glacial HOAc (0.1 mL) and MeOH (0.5 mL) and filtered. The filtrate was directly

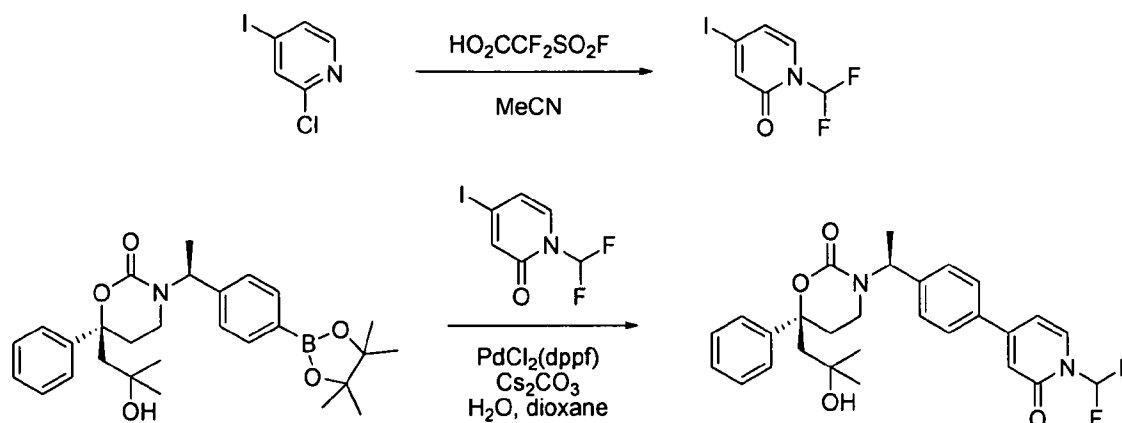
purified by prep HPLC to afford (S)-3-((S)-1-(4-(1-(difluoromethyl)-6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-6-(2-hydroxy-2-methylpropyl)-6-phenyl-1,3-oxazinan-2-one (11.8 mg, 57%) as an oil. LC-MS Method 1 t_R = 1.55 min, m/z = 497, 248; ^1H NMR ($CDCl_3$) 1.13 (s, 3H), 1.19 (s, 3H), 1.56 (d, 3H), 2.15-2.35 (s, 4H), 2.42 (m, 2H), 2.88 (m, 1H), 5.71 (q, 1H), 6.64 (d, 1H), 7.04 (d, 2H), 7.18 (d, 2H), 7.30-7.40 (5H), 7.52 (1H), 7.60 (m, 1H), 7.75 (t, 1H).

5-bromo-1-(difluoromethyl)pyridin-2(1H)-one was prepared as described in Ando, M.; Wada, T.; Sato, N. *Org. Lett.* **2006**, *8*, 3805-3808.

10

EXAMPLE 5

(S)-3-((S)-1-(4-(1-(difluoromethyl)-2-oxo-1,2-dihydropyridin-4-yl)phenyl)ethyl)-6-(2-hydroxy-2-methylpropyl)-6-phenyl-1,3-oxazinan-2-one



15 Step 1

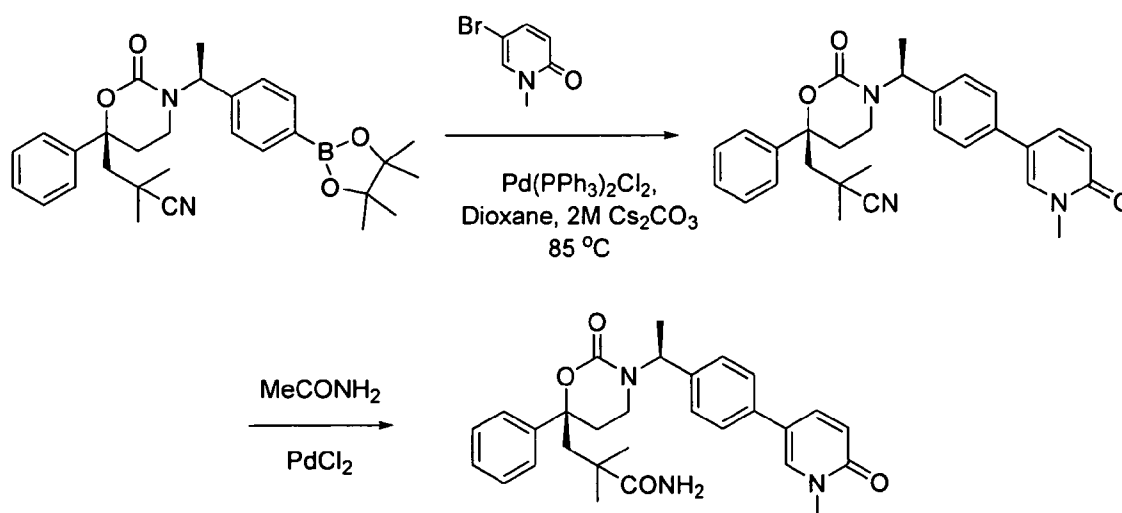
A stirred mixture of 2-chloro-4-iodopyridine (1.33 g, 5.6 mmol) and powdered $NaHCO_3$ (935 mg, 11.2 mmol) in MeCN (2 mL) was warmed to 40 °C in an oil bath and a solution of 2,2-difluoro-2-(fluorosulfonyl)acetic acid (0.57 mL, 5.6 mmol) in MeCN (10 mL) was added dropwise over 10 min. The mixture was stirred at 40 °C for 2 h. LC-MS showed partial conversion to desired product. Powdered $NaHCO_3$ (935 mg, 11.2 mmol) was added followed by a solution of 2,2-difluoro-2-(fluorosulfonyl)acetic acid (0.57 mL, 5.6 mmol) in MeCN (10 mL) dropwise over 10 min. The mixture was stirred at 40 °C for 2 h. The mixture was diluted with satd aq $NaHCO_3$ (25 mL) and concentrated under reduced pressure. The aqueous residue was extracted with EtOAc (90 mL). The organic extract was washed with brine (20 mL), dried over Na_2SO_4 and concentrated to afford an amber oil (1.14 g). Chromatography on a 40-g silica gel cartridge, eluted with a 0-40% EtOAc in hexanes gradient, afforded 1-(difluoromethyl)-4-iodopyridin-2(1H)-one (255 mg, yield 16%, estimated purity 45%) as yellow oil. LC-MS Method 1 t_R = 1.23 min, m/z = 272. The material was used without further purification.

Step 2

A microwave vial equipped with a flea stir bar was charged with (S)-6-(2-hydroxy-2-methylpropyl)-6-phenyl-3-((S)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl)-1,3-oxazinan-2-one (52 mg, 0.11 mmol), 1-(difluoromethyl)-4-iodopyridin-2(1H)-one (29 mg, 0.11 mmol), Cs₂CO₃ (71 mg, 0.22 mmol), H₂O (0.1 mL) and dry dioxane (1 mL). The mixture was sparged with N₂ for 5 min and PdCl₂(dppf) (5 mg, 0.007 mmol) was added. The mixture was sparged with N₂ for 5 min and heated at 110 °C in the microwave for 1 h. The mixture was diluted with 5% aq HCl (0.2 mL) and MeOH (2 mL) and filtered. The filtrate was directly purified by prep HPLC to afford a brown oil (16.2 mg) which was applied to a 2-g silica SPE cartridge which was eluted sequentially with 25 and 50% EtOAc in hexanes (15 mL of each) and EtOAc (3 x 15 mL) to afford five fractions. Fractions 3 and 4 were pooled and concentrated to afford (S)-3-((S)-1-(4-(1-(difluoromethyl)-2-oxo-1,2-dihydropyridin-4-yl)phenyl)ethyl)-6-(2-hydroxy-2-methylpropyl)-6-phenyl-1,3-oxazinan-2-one (13.4 mg, 25%) as a colorless oil. LC-MS Method 1 t_R = 1.57 min, m/z = 497, 439; ¹H NMR (CD₃OD) 0.96 (s, 3H), 1.27 (s, 3H), 1.56 (d, 3H), 2.15 (s, 2H), 2.21 (m, 1H), 2.40-2.60 (2H), 3.08 (m, 1H), 5.59 (q, 1H), 6.66 (s, 1H), 6.74 (d, 1H), 7.07 (d, 2H), 7.30-7.40 (5H), 7.45 (d, 2H), 7.77 (1H), 7.79 (t, 1H).

EXAMPLE 6

2,2-dimethyl-3-((R)-3-((S)-1-(4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)propanamide



25 Step 1

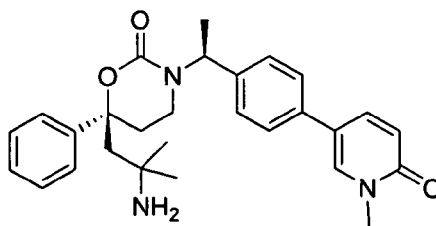
A mixture of 2,2-dimethyl-3-((*R*)-2-oxo-6-phenyl-3-((*S*)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl)-1,3-oxazinan-6-yl)propanenitrile (392 mg, 0.775 mmol), 5-bromo-1-methylpyridin-2(1*H*)-one (220 mg, 1.5 equiv), 2*M* aq Cs₂CO₃ solution (900 μ L), Pd(PPh₃)₂Cl₂ (40 mg, 7 mol%) and anhydrous 1,4-dioxane (8.5 mL) was degassed and refilled with N₂ gas 3 times. The mixture was then heated overnight at 85 °C under protection of N₂ gas. After being cooled to rt, the mixture was diluted with EtOAc (20 mL), washed by water (20 mL). The aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic layers were washed by water (10 mL), brine (2 x 10 mL) and dried over Na₂SO₄. After filtration and concentration, the residue was purified by Gilson to afford 34mg product (9% yield). LC-MS (3min. method) *t_R* = 1.44min., *m/z* 470 (*M*+1). ¹H NMR (CDCl₃) δ 7.68(dd, 1H), 7.52(d, 1H), 7.31(q, 2H), 7.16(d, 2H), 7.07(t, 2H), 6.97(d, 2H), 6.91(d, 1H), 5.66(q, 1H), 3.71(s, 3H), 2.99(dt, 1H), 2.47(dd, 2H), 2.27(m, 1H), 2.13(s, 2H), 1.55(d, 3H), 1.44(s, 3H), 1.24(s, 3H).

Step 2

A THF:H₂O (2mL, 3:1) solution of 2,2-dimethyl-3-((*R*)-3-((*S*)-1-(4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)propanenitrile (55 mg, 0.12 mmol), acetamide (177 mg, 3 mmol) and PdCl₂ (21 mg, 0.12 mmol) was stirred overnight. The solvent was removed and the crude material redissolved in CH₃CN. The crude product was purified via prep HPLC to afford 2,2-dimethyl-3-((*R*)-3-((*S*)-1-(4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)propanamide (28 mg). LC-MS Method 1 *t_R* = 1.25 min, *m/z* = 488 (*M*+1); ¹H NMR (CDCl₃) 7.55 (dd, 1H, *J* = 9Hz, 3Hz), 7.42 (d, 1H, *J* = 3Hz), 7.32 (d, 1H, *J* = 4 Hz), 7.29 (m, 4H), 7.14 (d, 2H, 8Hz), 7.00 (d, 2H, *J* = 8Hz), 6.79 (d, 1H, *J* = 9 Hz), 5.66 (q, 1H, *J* = 8Hz), 3.62 (s, 3H), 2.95-2.89 (m, 1H), 2.5 (d, 1H, *J* = 15 Hz), 2.26-2.1 (m, 3H), 2.2 (d, 1H, *J* = 15 Hz), 2.5 (d, 1H, *J* = 15 Hz), 2.26-2.10 (m, 3H), 2.2 (d, 1H, *J* = 15 Hz), 1.53 (d, 3H, *J* = 7Hz), 1.22 (s, 3H), 1.20 (s, 3H)

EXAMPLE 7

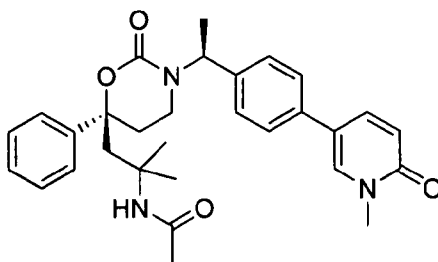
(*S*)-6-(2-amino-2-methylpropyl)-3-((*S*)-1-(4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one



A foil covered flask charged with 2,2-dimethyl-3-((*R*)-3-((*S*)-1-(4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)propanamide (20 mg, 0.04 mmol) in 1:1 CH₃CN/H₂O (1 mL) was treated with PhI(O₂CCF₃)₂ (31 mg, 0.07 mmol). The reaction was complete after 24 h. The solvent was removed and the crude material purified by prep HPLC to afford (*S*)-6-(2-amino-2-methylpropyl)-3-((*S*)-1-(4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one (16 mg). LC/MS ES+ = 460 (M+1). LC-MS Method 1 *t_R* = 1.06 min, *m/z* = 460 (M+1); ¹H NMR (CDCl₃) 7.60 (dd, 1H, *J* = 9Hz, 2Hz), 7.46 (d, 1H, *J* = 3Hz), 7.39-7.27 (m, 5H), 7.20 (d, 2H, *J* = 7 Hz), 7.1 (d, 2H, *J* = 8 Hz), 6.78 (d, 1H, *J* = 9Hz, 5.61 (q, 1H, *J* = 7Hz), 3.65 (s, 3H), 2.87 (m, 1H), 2.80 (d, 1H, *J* = 16Hz), 2.23 (d, 1H, *J* = 16 Hz), 2.19-2.08 (m, 3H), 1.54 (d, 3H, *J* = 7Hz), 1.41 (s, 3H), 0.96 (s, 3H).

EXAMPLE 8

N-(2-methyl-1-((*S*)-3-((*S*)-1-(4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)propan-2-yl)acetamide

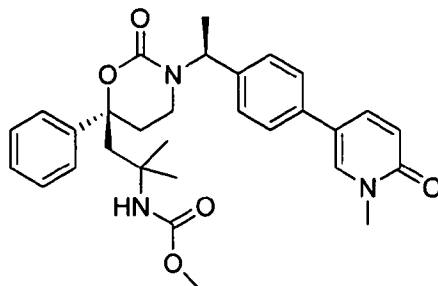


A CH₂Cl₂ (1 mL) solution of (*S*)-6-(2-amino-2-methylpropyl)-3-((*S*)-1-(4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one (5 mg, 0.009 mmol) was treated with DMAP (5mg, 0.04 mmol), *i*-Pr₂NEt (10 drops), and acetic anhydride (20 drops). The reaction was stirred overnight. The reaction solution was washed with water. The organic layer was evaporated and the crude material purified by prep HPLC affording *N*-(2-methyl-1-((*S*)-3-((*S*)-1-(4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)propan-2-yl)acetamide (0.88 mg). LC-MS Method 1 *t_R* = 1.3 min, *m/z* = 502 (M+1).

EXAMPLE 9

Methyl 2-methyl-1-((*S*)-3-((*S*)-1-(4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)propan-2-ylcarbamate

- 81 -

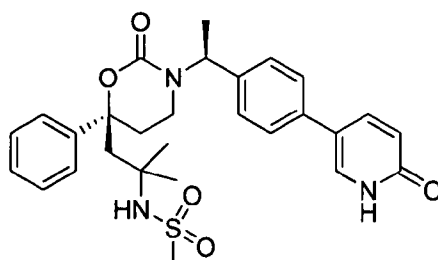


A CH_2Cl_2 (1 mL) solution of (S)-6-(2-amino-2-methylpropyl)-3-((S)-1-(4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one (5 mg, 0.009 mmol) was treated with DMAP (5mg, 0.04 mmol), $i\text{-Pr}_2\text{NEt}$ (10 drops), and methyl chloroformate (20 drops).

- 5 The reaction was stirred overnight. The reaction solution was by prep HPLC affording methyl 2-methyl-1-((S)-3-((S)-1-(4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)propan-2-ylcarbamate (2.58 mg). LC-MS Method 1 t_R = 1.45 min, m/z = 518 ($M+1$); ^1H NMR (CDCl_3) 7.66 (dd, 1H, J = 9Hz, 2Hz), 7.48 (d, 1H, J = 3Hz), 7.35-7.27 (m, 5H), 7.15 (d, 2H, J = 8 Hz), 7.01 (d, 2H, J = 8 Hz), 6.87 (d, 1H, J = 9Hz), 5.67 (q, 1H, J = 7 Hz), 3.69 (s, 3H), 2.2 (s, 3H), 1.54 (d, 3H, J = 7 Hz), 1.46- 1.36 (m, 2H), 1.30 (s, 3H), 1.20 (s, 3H).

EXAMPLE 10

N-(2-methyl-1-((S)-2-oxo-3-((S)-1-(4-(6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-6-phenyl-1,3-oxazinan-6-yl)propan-2-yl)methanesulfonamide



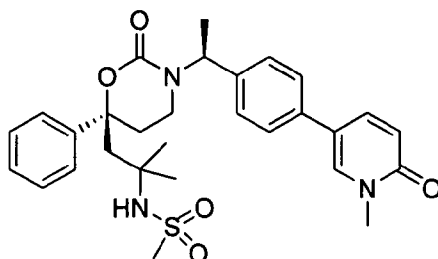
15 The title compound was prepared from N-(1-((S)-3-((S)-1-(4-bromophenyl)ethyl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)-2-methylpropan-2-yl)methanesulfonamide and 2-oxo-1,2-dihydropyridin-5-ylboronic acid following a procedure analogous to that described in Example 4. LC-MS Method 1 t_R = 1.3 min, m/z = 524 ($M+1$); ^1H NMR (CDCl_3) 7.81 (d, 1H, J = 9Hz), 7.63 (br s, 1H), 7.39-7.31 (m, 5H), 7.18 (d, 2H, J = 8Hz), 7.03 (d, 2H, J = 7 Hz), 6.79 (d, 1H, J = 9 Hz), 5.67 (q, 1H, J = 6Hz), 2.93 (s, 3H), 2.90 (m, 1H), 2.49 (d, 1H, J = 15 Hz), 2.32 (d, 1H, J = 15 Hz), 2.28-2.18 (m, 3H), 1.54 (d, 3H, J = 7Hz), 1.36 (s, 3H), 1.25 (s, 3H).

25 N-(1-((S)-3-((S)-1-(4-bromophenyl)ethyl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)-2-methylpropan-2-yl)methanesulfonamide was prepared from 3-((R)-3-((S)-1-(4-bromophenyl)ethyl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)-2,2-dimethylpropanenitrile by sequential

application of procedures analogous to those described in Examples 6 Step 2, Example 7 and Example 11.

EXAMPLE 11

5 N-(2-methyl-1-((S)-3-((S)-1-(4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)propan-2-yl)methanesulfonamide

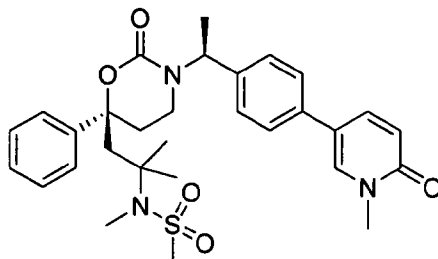


A CH₂Cl₂ (1 mL) solution of (S)-6-(2-amino-2-methylpropyl)-3-((S)-1-(4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one (5 mg, 0.009 mmol) was
 10 treated with DMAP (5mg, 0.04 mmol), i-Pr₂NEt (10 drops), and MsCl (20 drops). The reaction was stirred overnight. The reaction solution was washed with water. The organic layer was evaporated and the crude material purified by prep HPLC affording N-(2-methyl-1-((S)-3-((S)-1-(4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)propan-2-yl)methanesulfonamide (3.30 mg). LC-MS Method 1 t_R = 1.39 min, m/z = 538 (M+1);
 15 ¹H NMR (CDCl₃) 7.61 (dd, 1H, J = 9Hz, 3Hz), 7.46 (d, 1H, J = 2Hz), 7.40-7.27 (m, 5H), 7.17 (d, 2H, J = 8Hz), 7.04 (d, 2H, J = 8Hz), 6.79 (d, 1H, J = 9Hz), 5.67 (q, 1H, J = 7 Hz), 3.66 (s, 3H), 2.93 (s, 3H), 2.31-2.22 (m, 2H), 1.55 (d, 3H, J = 7Hz), 1.48-1.36 (m, 2H), 1.33 (s, 3H), 1.24 (s, 3H).

20

EXAMPLE 12

N-methyl-N-(2-methyl-1-((S)-3-((S)-1-(4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)propan-2-yl)methanesulfonamide

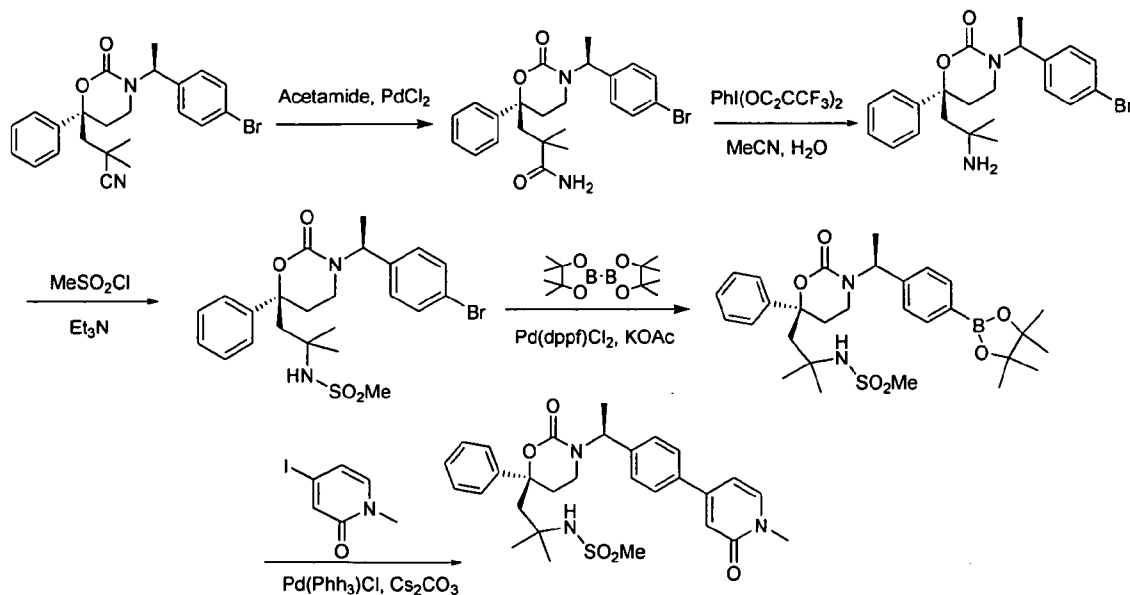


To a rt solution of N-(2-methyl-1-((S)-2-oxo-3-((S)-1-(4-(6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-6-phenyl-1,3-oxazinan-6-yl)propan-2-yl)methanesulfonamide (7 mg, 0.013 mmol)
 25 in THF, NaH (10 mg, 0.20 mmol) was added followed by methyl iodide (30 uL, 0.080 mmol). The

reaction was heated to 60 °C for 5 h. The flask was cooled to rt then to 0 °C before quenching with satd aq NH₄Cl. The mixture was extracted with EtOAc (3x) and the combined organic layers were dried over Na₂SO₄, filtered, evaporated and purified by prep HPLC to afford *N*-methyl-*N*-(2-methyl-1-((*S*)-3-((*S*)-1-(4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)propan-2-yl)methanesulfonamide (4.63 mg). LC-MS Method 1 *t_R* = 1.45 min, *m/z* = 552 (*M*+1); ¹H NMR (CDCl₃) 7.55 (dd, 1H, *J* = 9Hz, 3Hz), 7.41 (d, 1H, *J* = 3 Hz), 7.35 -7.27 (m, 5H), 7.13 (d, 2H, *J* = 8Hz), 6.98 (d, 2H, *J* = 8Hz), 6.79 (d, 1H, *J* = 9 Hz), 6.55 (q, 1H, *J* = 7Hz), 3.62 (s, 3H), 2.91-2.86 (m, 1H), 2.86 (s, 3H), 2.73 (d, 1H, *J* = 15 Hz), 2.74 (s, 3H), 2.46 (d, 1H, *J* = 15Hz), 2.39 -2.36 (m, 2H), 2.25-2.16 (m, 1H), 1.53 (d, 3H, *J* = 7 Hz), 1.53 (s, 3H), 1.22 (s, 3H).

EXAMPLE 13

N-(2-methyl-1-((*S*)-3-((*S*)-1-(4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)phenyl)ethyl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)propan-2-yl)methanesulfonamide



Step 1

To a solution of 3-(*R*-3-*S*-1-(4-bromophenyl)-ethyl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)-2,2-dimethylpropanenitrile (1 g, 2.27 mmol) in a mixture of THF/H₂O (3:1, 10 mL) was added acetamide (3.35 g, 56.75 mmol) and PdCl₂ (0.402 g, 2.27 mmol). The reaction was stirred overnight. The solvent was removed, and the residue was purified by TLC to afford 3-(*R*-3-*S*-1-(4-bromophenyl)-ethyl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)-2,2-dimethylpropanamide (0.745 g, 71.6%).

Step 2

To a solution of 3-(*R*-3-*S*-1-(4-bromophenyl)-ethyl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)-2,2-dimethylpropanamide (0.74 g, 1.612 mmol) in a mixture of CH₃CN/H₂O (20 mL, 1:1) was added PhI(OC₂CCF₃)₂ (1.178 g, 2.74 mmol). The mixture reaction was stirred overnight. The mixture was extracted with EtOAc (30 mL). The organic layer was washed with brine, and concentrated to afford *S*-6-(2-amino-2-methylpropyl)-3-*S*-1-(4-bromophenyl)-ethyl)-6-phenyl-1,3-oxazinan-2-one (0.6 g, 87%).

Step 3

To a solution of *S*-6-(2-amino-2-methylpropyl)-3-*S*-1-(4-bromophenyl)-ethyl)-6-phenyl-1,3-oxazinan-2-one (0.6 g, 1.39 mmol) in CH₂Cl₂ (10 mL) was added Et₃N (0.84 g, 8.34 mmol). The mixture was cooled at 0 °C, MsCl (0.48 g, 4.17 mmol) was added. The reaction was stirred at rt for 1 h. The mixture was evaporated to afford the crude product. The residue was purified by column to afford *N*-1-*S*-3-*S*-1-(4-bromophenyl)-ethyl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)-2-methylpropan-2-yl)-methyl-sulfonamide (0.5 g, 70.4%).

Step 4

To a solution of *N*-1-*S*-3-*S*-1-(4-bromophenyl)ethyl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)-2-methylpropan-2-yl)-methyl-sulfonamide (0.5 g, 0.98 mmol) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi-(1,3,2-dioxaborolane) (0.399 g, 1.57 mmol) in dry DMSO (15 mL) was added KOAc (0.31 g, 3.14 mmol) and Pd(dppf)Cl₂ (0.025 g, 0.03 mmol) under N₂ atmosphere. After addition, the mixture was stirred at 90 °C overnight. After TLC showed the starting material had disappeared, the solid was filtered off. Water (30 mL) and EtOAc (50 mL) was added, the mixture was extracted with EtOAc (3 x 30 mL). The combined organic layer was washed with brine (50 mL), dried over Na₂SO₄, filtered, and concentrated to dryness. The residue was purified by column chromatography to afford *N*-(2-methyl-1-*S*-2-oxo-6-phenyl-3-*S*-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl)-1,3-oxazinan-6-yl)propan-2-yl)-methyl-sulfonamide (0.2 g, yield: 37%).

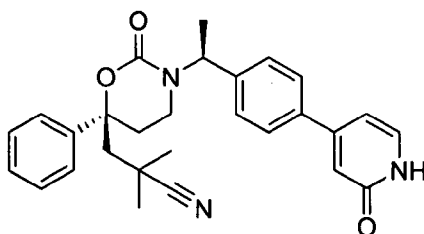
Step 5

To a solution of *N*-(2-methyl-1-*S*-2-oxo-6-phenyl-3-*S*-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl)-1,3-oxazinan-6-yl)propan-2-yl)-methyl sulfonamide (150 mg, 0.27 mmol) and 4-iodo-1-methylpyridin-2(1*H*)-one in dry 1,4-dioxane (5 mL) was added Cs₂CO₃ (0.3 mL, 6 mmol) and Pd(PPh₃)Cl₂ (20 mg). After addition, the mixture was warmed at 110 °C for 2 min. After TLC showed the starting material had disappeared, the solid was filtered off. Water (20 mL) and EtOAc (30 mL) were added. The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layer was washed with brine, dried over Na₂SO₄, filtered, and concentrated to give the crude product, which was purified by

preparative HPLC to provide *N*-2-methyl-1-*S*-3-*S*-1-4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)-phenyl)-ethyl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl) propan-2-yl) methyl sulfonamide (20 mg, 14%). LC-MS Method 2 t_R = 1.154 min, m/z = 538.1; ^1H NMR ($CDCl_3$): δ 1.25 (s, 3H), 1.32 (s, 3H), 1.55 (d, 3H), 2.50 (d, 2H), 2.91 (s, 3H), 3.63 (s, 3H), 4.54 (b, 1H), 5.67 (m, 1H), 6.53 (d, 1H), 6.92 (s, 1H), 7.06 (d, 2H), 7.30-7.50 (m, 8H).

EXAMPLE 14

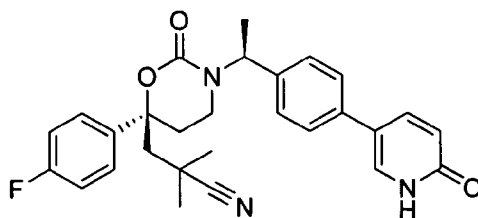
2,2-dimethyl-3-((*R*)-2-oxo-3-((*S*)-1-(4-(2-oxo-1,2-dihydropyridin-4-yl)phenyl)ethyl)-6-phenyl-1,3-oxazinan-6-yl)propanenitrile



The title compound was prepared from 2,2-dimethyl-3-((*R*)-2-oxo-6-phenyl-3-((*S*)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl)-1,3-oxazinan-6-yl)propanenitrile and 4-iodopyridin-2(1H)-one following a procedure analogous to that described in Example 4. LC-MS Method 1 t_R = 1.36 min, m/z = 456($M+1$); ^1H NMR ($CDCl_3$) 7.77(d, 1H), 7.43-7.32(m, 7H), 7.01(t, 4H), 5.67(q, 1H), 2.99(dd, 1H), 2.57-2.43(m, 2H), 2.32(m, 1H), 2.17(s, 2H), 1.57(d, 3H), 1.40(s, 3H), 1.33(s, 3H).

EXAMPLE 15

3-((*R*)-6-(4-fluorophenyl)-2-oxo-3-((*S*)-1-(4-(6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-1,3-oxazinan-6-yl)-2,2-dimethylpropanenitrile



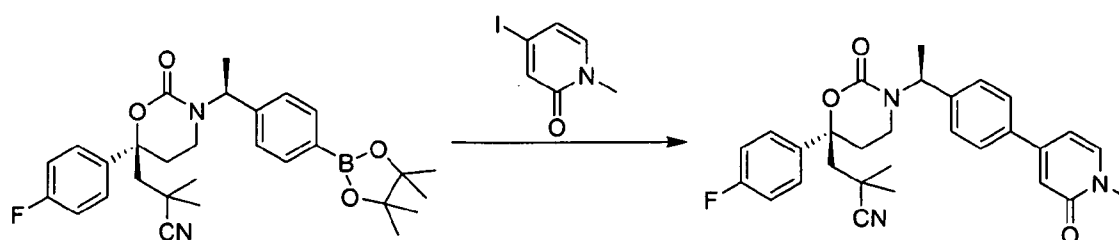
The title compound was prepared from 3-((*R*)-3-((*S*)-1-(4-bromophenyl)ethyl)-6-(4-fluorophenyl)-2-oxo-1,3-oxazinan-6-yl)-2,2-dimethylpropanenitrile and 2-oxo-1,2-dihydropyridin-5-ylboronic acid following a procedure analogous to that described in Example 4. LC-MS Method 1 t_R = 1.37 min, m/z = 474($M+1$); ^1H NMR ($CDCl_3$) 7.97, (dd, 1H), 7.73(s, 1H), 7.33(m, 2H),

- 86 -

7.20(d, 2H), 7.17(t, 2H), 6.98(m, 3H), 5.67(q, 1H), 3.00(dt, 1H), 2.49(m, 2H), 2.30(m, 1H), 2.13(s, 2H), 1.55(d, 3H), 1.45(s, 3H), 1.34(s, 3H).

EXAMPLE 16

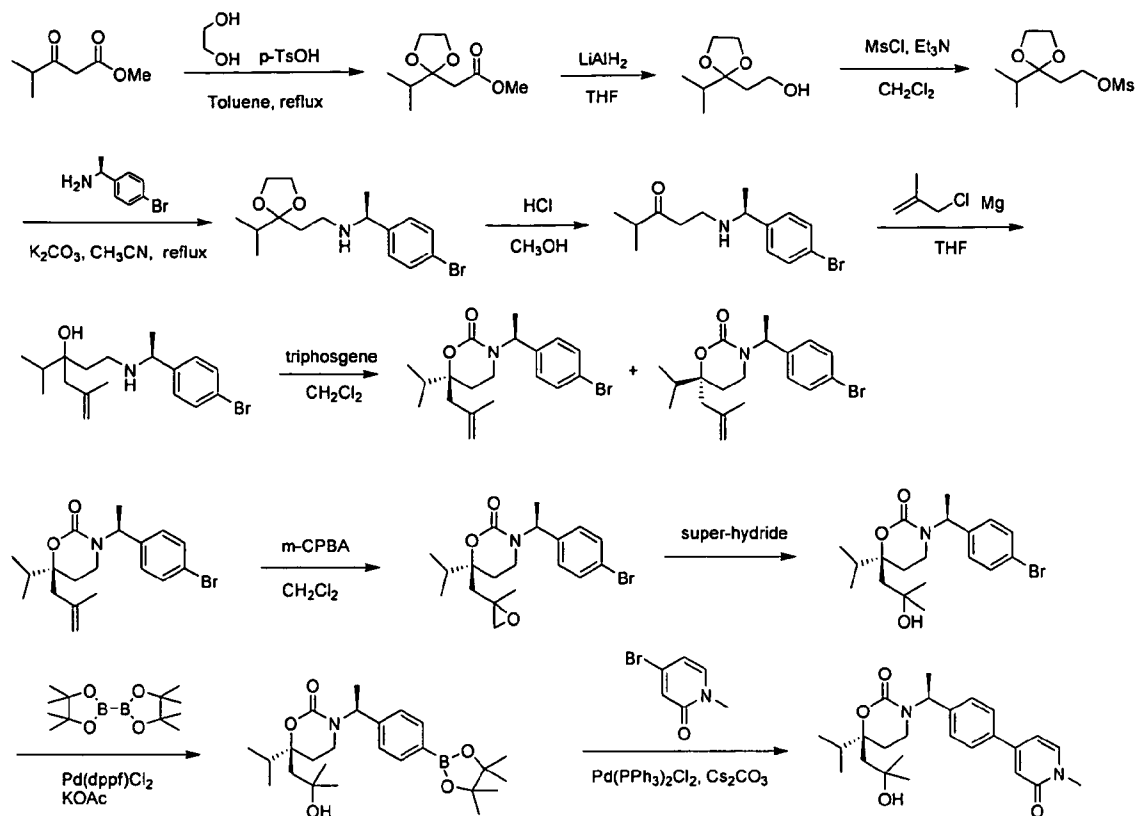
- 5 3-((R)-6-(4-fluorophenyl)-3-((S)-1-(4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)phenyl)ethyl)-2-oxo-1,3-oxazinan-6-yl)-2,2-dimethylpropanenitrile



- A mixture of 3-((R)-6-(4-fluorophenyl)-2-oxo-3-((S)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl)-1,3-oxazinan-6-yl)-2,2-dimethylpropanenitrile (100mg, 0.21mmol) and 4-iodo-1-methyl-1H-pyridin-2-one (40 mg, 0.17 mmol), Pd(PPh₃)₂Cl₂ (20 mg), and aq. Cs₂CO₃ solution (2.0 mL, 2M) in 1,4-dioxane (5 mL) was stirred at reflux for 2 h. The organic phase was separated and concentrated to give the crude product, which was purified by preparative TLC to give 3-((R)-6-(4-fluorophenyl)-3-((S)-1-(4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)phenyl)ethyl)-2-oxo-1,3-oxazinan-6-yl)-2,2-dimethylpropanenitrile (55 mg, 66%). LC-MS Method 2 t_R = 1.096 min, m/z = 488.3; ¹H NMR (CDCl₃): δ 1.27 (s, 3H), 1.40 (s, 3H), 1.48 (d, 3H), 2.06 (s, 2H), 2.23 (m, 1H), 2.41 (m, 2H), 2.90 (m, 1H), 3.51 (s, 3H), 5.60 (m, 1H), 6.27 (m, 1H), 6.65 (d, 1H), 6.89 (d, 2H), 6.99 (t, 2H), 7.26 (m, 5H).

EXAMPLE 17

- 6-(2-hydroxy-2-methylpropyl)-6-isopropyl-3-((S)-1-(4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)phenyl)ethyl)-1,3-oxazinan-2-one



Step 1

To a solution of methyl 4-methyl-3-oxopentanoate (72 g, 0.5 mol), and ethylene glycol (56 g, 1 mol) in toluene (500 mL) was added 4-methylbenzenesulfonic acid (1.9 g, 0.01 mol). The mixture was stirred at reflux with a Dean-Stark trap to remove water. The reaction mixture was washed with a small amount of water and brine, dried over anhydrous Na_2SO_4 , and concentrated in vacuum to give the crude methyl 2-(2-isopropyl-1,3-dioxolan-2-yl)-acetate (67 g 71% yield), which was used for the next step without further purification.

Step 2

In a flame-dried three neck flask equipped with an addition funnel, magnetic stirring bar, rubber septum, and a nitrogen inlet, was placed LiAlH_4 (3.12 g, 82.1 mmol) and THF (700 mL). After being cooled at 0 °C, a solution of methyl 2-(2-isopropyl-1,3-dioxolan-2-yl) acetate (12 g, 63.8 mmol) in THF (160 mL) was added dropwise with stirring. The mixture was warmed to rt, and stirred for 24 hours. The reaction was quenched by adding water (5 mL), 15% aqueous NaOH (10 mL), and water (5 mL) slowly. The organic layer was separated, and the residue was extracted with EtOAc (3×100 mL). The combined organic phase was dried over Na_2SO_4 , and concentrated to afford the crude product, which was purified by column chromatography to give

2-(2-isopropyl-1,3-dioxolan-2-yl)-ethanol (6.8 g, 67%). ^1H NMR (CDCl_3): δ 0.90 (d, J = 6.8 Hz, 6H), 1.87-1.96 (m, 3H), 2.81 (br, 1H), 3.69-3.72 (m, 2H), 3.92-4.01 (m, 4H).

Step 3

5 To a solution of 2-(2-isopropyl-1,3-dioxolan-2-yl)-ethanol (8.0 g, 50 mmol) and triethylamine (23.5 mL, 170 mmol) in anhydrous CH_2Cl_2 (120 mL) was added methanesulfonyl chloride (11.6 mL, 150 mmol) at 0 °C, and the reaction mixture was stirred at rt till the reaction was finished. The reaction mixture was washed with water and brine, dried over Na_2SO_4 , filtered, and concentrated to give the crude 2-(2-isopropyl-1,3-dioxolan-2-yl)ethyl methanesulfonate (12 g, 10 crude), which was used for the next step without further purification.

Step 4

To a solution of 2-(2-isopropyl-1,3-dioxolan-2-yl)ethyl methanesulfonate (12 g, 50 mmol) and (S)-1-(4-methoxyphenyl)-ethyl amine (19.9 g, 100 mmol) in CH_3CN (250 mL) was added 15 K_2CO_3 (8 g, 58 mmol), and the mixture was refluxed for 10 h. The solution was filtered, and the filtrate was concentrated to afford the crude product, which was purified by column chromatography to give (S)-1-(4-bromophenyl)-N-(2-(2-isopropyl-1,3-dioxolan-2-yl)ethyl)ethanamine (6.5 g, 38% yield).

20 Step 5

To a solution of (S)-1-(4-bromophenyl)-N-(2-(2-isopropyl-1,3-dioxolan-2-yl)ethyl)ethanamine (6.5 g, 19 mmol) in MeOH (60 mL) was added conc HCl (60 mL). The mixture was stirred at 65 °C till the reaction was finished. The mixture was cooled to 0 °C, and the pH of the mixture was adjusted to 7 by adding the satd aq NaHCO_3 . The mixture was 25 concentrated, and the residue was extracted with EtOAc (3×100 mL). The organic layer was washed with brine, dried over Na_2SO_4 , and concentrated to give (S)-1-(1-(4-bromophenyl)ethylamino)-4-methylpentan-3-one (5.5 g, 97% yield), which was used for the next step without further purification. ^1H NMR (CDCl_3): δ 1.07 (d, J = 6.8 Hz, 6H), 1.29 (d, J = 6.4 Hz, 3H), 1.89 (br, 1H), 2.54-2.62 (m, 4H), 2.66-2.69 (m, 1H), 3.68-3.72 (m, 1H), 7.18-7.20 (m, 2H), 30 7.41-7.44 (m, 2H).

Step 6

To a suspension of Mg (11g, 458 mmol) and I_2 (0.5g) in anhydrous THF (50 mL) was added 3-chloro-2-methylprop-1-ene (1 mL) to initiate the reaction. THF (300 mL) was added, 35 more solution of 3-chloro-2-methylprop-1-ene (15 mL) in THF (20 mL) was dropped into the reaction at 0 °C under N_2 over 30 min. A solution of (S)-1-(1-(4-bromophenyl)-ethyl amino)-4-methylpentan-3-one (5g) in THF (50mL) was added dropwise at -78 °C over 45 min. The reaction

was stirred at rt for 2 h, cautiously quenched with satd aq NH_4Cl , and filtered. The filtrate was extracted with EtOAc ($3 \times 100 \text{ mL}$), washed with brine, dried over anhydrous Na_2SO_4 , and concentrated in vacuo to give 1-(S-1-(4-bromophenylamino)-3-isopropyl-5-methylhex-5-en-3-ol (6.4 g, 90% yield), which was used for the next step without further purification.

5

Step 7

To a solution of 1-(S-1-(4-bromophenylamino)-3-isopropyl-5-methylhex-5-en-3-ol (6.4 g, 16.8 mmol) and triethylamine (5.34 g, 52 mmol) in CH_2Cl_2 (260 mL) was added triphosgene (2.52 g, 8.5 mmol) at 0°C under N_2 , and the mixture was stirred at rt overnight. The reaction mixture was quenched with water, and extracted with CH_2Cl_2 ($3 \times 50 \text{ mL}$). The combined organic layer was washed with brine, dried over Na_2SO_4 , filtered, and concentrated to afford the crude product, which was purified by column chromatography to give two isomers of 3-((S)-1-(4-bromophenyl)ethyl)-6-isopropyl-6-(2-methylallyl)-1,3-oxazinan-2-one.

Isomer 1: (1.85 g, 27% yield) ^1H NMR (CDCl_3): δ 0.83(d, $J = 7.2 \text{ Hz}$, 3H), 0.89 (d, $J = 7.2 \text{ Hz}$, 3H), 1.45 (d, $J = 6.8 \text{ Hz}$, 3H), 1.64-1.70 (m, 2H), 1.79 (s, 3H), 1.88-1.95 (m, 1H), 2.20-2.34 (m, 2H), 2.59-2.65 (m, 1H), 3.01-3.08 (m, 1H), 4.70 (s, 1H), 4.87 (s, 1H), 5.68-5.77 (m, 1H), 7.14 (d, $J = 8.4 \text{ Hz}$, 2H), 7.41 (d, $J = 8.4 \text{ Hz}$, 2H).

Isomer 2: (1.25g, 18% yield) ^1H NMR (CDCl_3): δ 0.87 (d, $J = 6.8 \text{ Hz}$, 3H), 0.92(d, $J = 6.8 \text{ Hz}$, 3H), 1.50 (d, $J = 7.2 \text{ Hz}$, 3H), 1.60-1.66 (m, 1H), 1.78 (s, 3H), 1.73-1.79 (m, 1H), 1.78-2.05 (m, 1H), 2.08 (d, $J = 14.0 \text{ Hz}$, 1H), 2.30 (d, $J = 14.0 \text{ Hz}$, 1H), 2.62-2.68 (m, 1H), 2.98-3.05 (m, 1H), 4.64 (s, 1H), 4.84 (s, 1H), 5.70-5.75 (m, 1H), 7.13 (d, $J = 8.4 \text{ Hz}$, 2H), 7.40 (d, $J = 8.4 \text{ Hz}$, 2H).

Step 8

To a solution of 3-((S)-1-(4-bromophenyl)ethyl)-6-isopropyl-6-(2-methylallyl)-1,3-oxazinan-2-one isomer 1 (500 mg, 1.32 mmol) in dry CH_2Cl_2 (64 mL) was added *m*-CPBA (455 g, 2.64 mmol) at rt. The reaction mixture was stirred until the starting material was consumed (monitored by TLC). The mixture was diluted with $(\text{CH}_3)_3\text{COCH}_3$ (70 mL), washed with 30% $\text{Na}_2\text{S}_2\text{O}_3$, and aq NaHCO_3 (3 x), dried over Na_2SO_4 , filtered, and concentrated to give 3-((S)-1-(4-bromophenyl)ethyl)-6-isopropyl-6-((2-methyloxiran-2-yl)methyl)-1,3-oxazinan-2-one isomer 1 (520 mg, 99%), which was used directly for the next step without further purification.

Step 9

To a solution of 3-((S)-1-(4-bromophenyl)ethyl)-6-isopropyl-6-((2-methyloxiran-2-yl)methyl)-1,3-oxazinan-2-one isomer 1 (520 mg, 1.32 mmol) in THF (32 mL) was added dropwise LiEt_3BH (Super-Hydride, 13.6 mL, 13.6 mmol) at 0°C under N_2 over 30 min., the resulting solution was stirred at $10-13^\circ\text{C}$ for 21.5 h. To the mixture was added H_2O_2 (40 mL).

The resulting solution was diluted with (CH₃)₃COCH₃ (380 mL), and washed with water, 30% aq Na₂S₂O₃, and brine. The organic phase was dried over Na₂SO₄, and filtered. The filtrate was concentrated to give the crude product, which was purified by column chromatography to afford 3-((S)-1-(4-bromophenyl)ethyl)-6-(2-hydroxy-2-methylpropyl)-6-isopropyl-1,3-oxazinan-2-one isomer 1 (320 mg, 61%). ¹H NMR (CDCl₃): δ 0.82 (d, *J* = 6.8 Hz, 3H), 0.95 (d, *J* = 6.8 Hz, 3H), 1.31 (s, 3H), 1.34 (s, 3H), 1.51 (d, *J* = 10.0 Hz, 3H), 1.61 (d, *J* = 15.2 Hz, 1H), 1.78-1.84 (m, 1H), 1.91 (d, *J* = 15.2 Hz, 1H), 2.02-2.15 (m, 2H), 2.36 (br, 1H), 2.62-2.68 (m, 1H), 3.03-3.09 (m, 1H), 5.73 (t, *J* = 7.2 Hz, 1H), 7.17-7.19 (m, 2H), 7.44-7.48 (m, 2H).

10 Step 10

To a solution of 3-((S)-1-(4-bromophenyl)ethyl)-6-(2-hydroxy-2-methylpropyl)-6-isopropyl-1,3-oxazinan-2-one isomer 1 (315 mg, 0.793 mmol) in DMSO (10 mL) was added 4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (602 mg, 2.38 mmol), CH₃CO₂K (770 mg, 79.3 mmol), Pd(dppf)₂Cl₂ (50 mg, 0.06 mmol) under N₂, the reaction was stirred at 90 °C for 4 h. The mixture was quenched with NH₄Cl, and extracted with EtOAc, washed with water and brine. The organic phase was dried over Na₂SO₄ and filtered. The filtrate was concentrated to give the crude product, which was purified by preparative TLC to give 6-(2-hydroxy-2-methylpropyl)-6-isopropyl-3-((S)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl)-1,3-oxazinan-2-one isomer 1 (250 mg, 71%).

20 Step 11

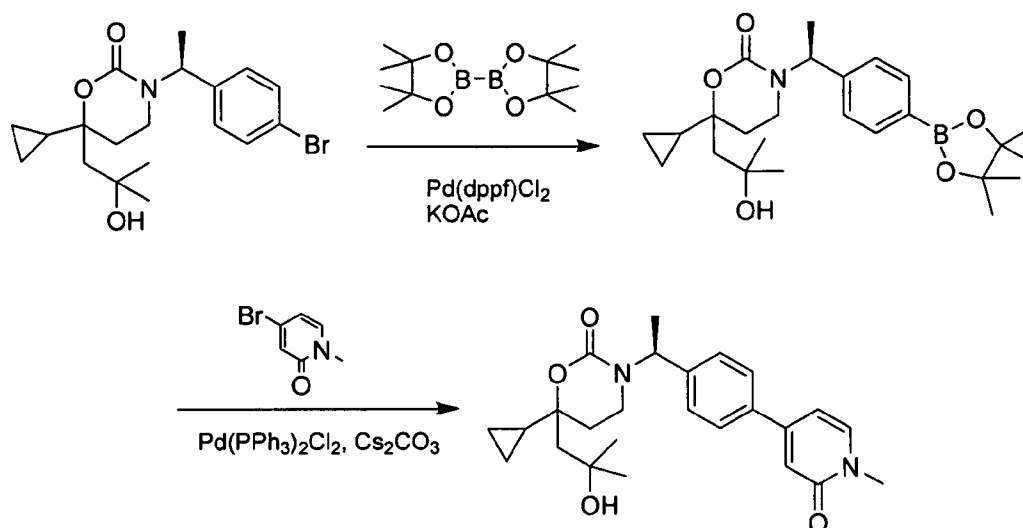
To a solution of 6-(2-hydroxy-2-methylpropyl)-6-isopropyl-3-((S)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl)-1,3-oxazinan-2-one isomer 1 (250 mg, 0.39 mmol), 4-bromo-1-methylpyridin-2(1H)-one (127 mg, 0.68 mmol), Cs₂CO₃ (2N, 4 mL) in 1,4-dioxane (20 mL) was added Pd(PPh₃)₂Cl₂ (54 mg, 0.056 mmol) under N₂. The reaction mixture was refluxed for 2h, quenched with water, and extracted with EtOAc. The organic phase was washed with H₂O and brine, dried over Na₂SO₄, and filtered. The filtrate was concentrated to give the crude product, which was purified by preparative TLC and preparative HPLC to afford 6-(2-hydroxy-2-methylpropyl)-6-isopropyl-3-((S)-1-(4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)phenyl)ethyl)-1,3-oxazinan-2-one isomer 1 (79 mg, 47% yield). LC-MS Method 2 *t_R* = 1.023 min, *m/z* = 427.6; ¹H NMR (CDCl₃) 0.85 (d, 3H), 0.96 (d, 3H), 1.26 (s, 3H), 1.28 (s, 3H), 1.54 (m, 4H), 1.84-1.88 (m, 2H), 2.04 (br, 1H), 2.01-2.18 (m, 2H), 2.75 (m, 1H), 3.10 (m, 1H), 3.52 (s, 3H), 5.80 (t, 1H), 6.37 (m, 1H), 6.74 (m, 1H), 7.28 (m, 1H), 7.25-7.37 (m, 2H), 7.50 (m, 2H).

6-(2-hydroxy-2-methylpropyl)-6-isopropyl-3-((S)-1-(4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)phenyl)ethyl)-1,3-oxazinan-2-one isomer 2 was prepared from 3-((S)-1-(4-bromophenyl)ethyl)-6-isopropyl-6-(2-methylallyl)-1,3-oxazinan-2-one isomer 2 following

procedures analogous to those described in Steps 8 - 11 above. LC-MS Method 2 t_R = 1.023 min, m/z = 427.6; ^1H NMR (CDCl_3) 0.79 (d, 3H), 0.92 (d, 3H), 1.27 (s, 3H), 1.30 (s, 3H), 1.51 (d, 3H), 1.58 (d, 1H), 1.73-1.81 (m, 1H), 1.88 (d, 1H), 2.0 (br, 1H), 2.04-2.08 (m, 2H), 2.65-2.68 (m, 1H), 3.04-3.07 (m, 1H), 3.52 (s, 3H), 5.75 (t, 1H), 6.37 (m, 1H), 6.74 (m, 1H), 7.21-7.35 (m, 3H), 7.51 (m, 2H).

EXAMPLE 18

6-cyclopropyl-6-(2-hydroxy-2-methylpropyl)-3-((S)-1-(4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)phenyl)ethyl)-1,3-oxazinan-2-one



The two diastereomers of 3-((S)-1-(4-bromophenyl)ethyl)-6-cyclopropyl-6-(2-hydroxy-2-methylpropyl)-1,3-oxazinan-2-one were prepared from methyl 3-cyclopropyl-3-oxopropanoate following procedures analogous to those described in Example 17 Steps 1 - 7. The title compound was prepared as follows.

Step 1

To a solution of 3-((S)-1-(4-bromophenyl)ethyl)-6-cyclopropyl-6-(2-hydroxy-2-methylpropyl)-1,3-oxazinan-2-one isomer 1 (230 mg, 0.58 mmol) in DMSO (15 mL) was added 4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)-1,3,2-dioxaborolane (450 mg, 1.77 mmol), $\text{CH}_3\text{CO}_2\text{K}$ (800 mg, 8.16 mmol), $\text{Pd}(\text{pddf})_2\text{Cl}_2$ (50 mg, 0.06 mmol) under N_2 . The reaction was stirred at 90°C for 34 h, quenched with NH_4Cl , and extracted with EtOAc. The organic phase was washed with water and brine, dried over Na_2SO_4 , and filtered. The filtrate was concentrated to give the crude product, which was purified by preparative TLC to give 6-cyclopropyl-6-(2-hydroxy-2-methylpropyl)-3-((S)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl)-1,3-oxazinan-2-one isomer 1 (140 mg, 54.3%).

Step 2

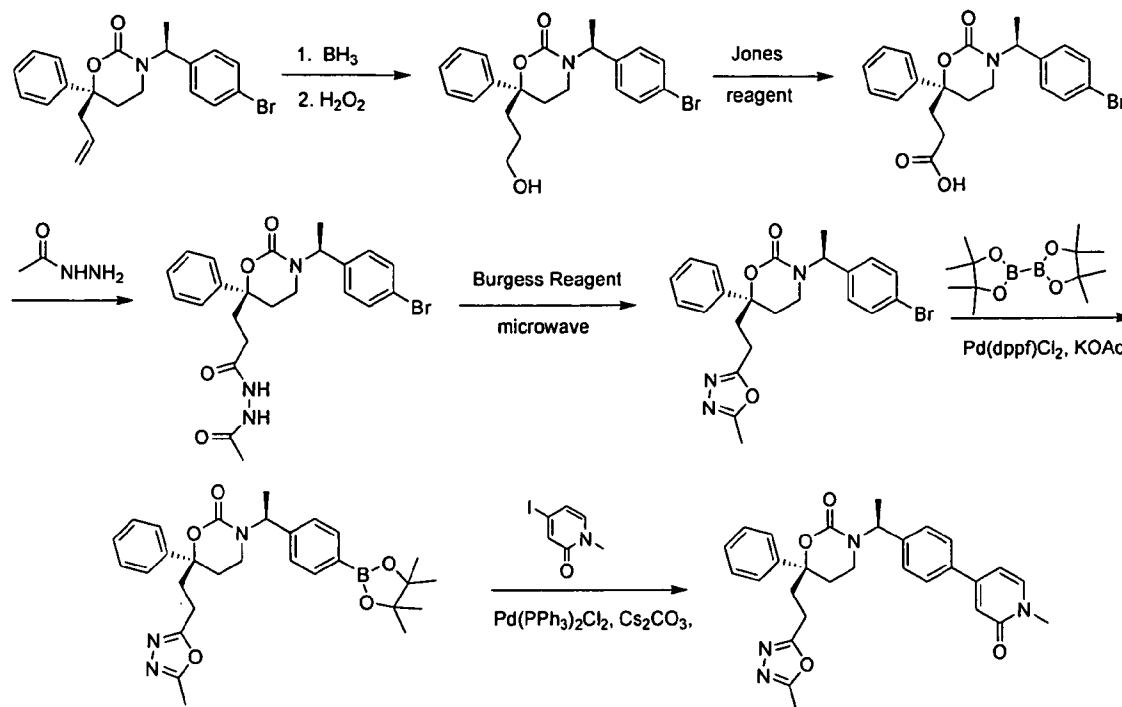
To a solution of 6-cyclopropyl-6-(2-hydroxy-2-methylpropyl)-3-((S)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl)-1,3-oxazinan-2-one isomer 1 (140 mg, 0.316 mmol), 4-bromo-1-methylpyridin-2(1H)-one (74.3 mg, 0.316 mmol), 2 M aq Cs₂CO₃ (3 mL) in 1,4-dioxane (20 mL) was added Pd(dppf)₂Cl₂ (30 mg, 0.043 mmol) under N₂. The reaction mixture was refluxed for 2h, quenched with water, and extracted with EtOAc. The organic phase was washed with H₂O and brine, dried over Na₂SO₄, and filtered. The filtrate was concentrated to give the crude product, which was purified by preparative TLC and preparative HPLC to afford 6-cyclopropyl-6-(2-hydroxy-2-methylpropyl)-3-((S)-1-(4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)phenyl)ethyl)-1,3-oxazinan-2-one isomer 1 (49.5 mg, 37.7%). LC-MS Method 2 t_R = 1.016 min, m/z = 367.2; ¹H NMR (CDCl₃) 0.50 (m, 2H), 0.62 (m, 2H), 0.97 (m, 1H), 1.32 (m, 6H), 1.58 (d, 3H), 1.97 (m, 3H), 2.28 (m, 1H), 2.78 (m, 1H), 3.40 (m, 1H), 3.58 (s, 3H), 5.85 (m, 1H), 6.41 (d, 1H), 6.79 (s, 1H), 7.33 (d, 1H), 7.41 (d, 1H), 7.56 (d, 1H)

6-cyclopropyl-6-(2-hydroxy-2-methylpropyl)-3-((S)-1-(4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)phenyl)ethyl)-1,3-oxazinan-2-one isomer 2 was prepared from 3-((S)-1-(4-bromophenyl)ethyl)-6-cyclopropyl-6-(2-hydroxy-2-methylpropyl)-1,3-oxazinan-2-one isomer 2 following procedures analogous to those described in Steps 1 and 2 immediately above. LC-MS Method 2 t_R = 0.99 min, m/z = 367.1; ¹H NMR (CDCl₃) 0.02 (m, 3H), 0.23 (m, 1H), 0.51 (m, 1H), 0.96 (s, 6H), 1.17 (d, 3H), 1.40-1.60 (m, 4H), 1.94 (m, 1H), 2.55 (m, 1H), 2.73 (m, 1H), 3.20 (s, 3H), 5.41 (m, 1H), 6.03 (d, 1H), 6.40 (s, 1H), 6.98 (m, 1H), 7.03 (m, 2H), 7.18 (m, 2H)

EXAMPLE 19

(R)-6-(2-(5-methyl-1,3,4-oxadiazol-2-yl)ethyl)-3-((S)-1-(4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)phenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one

- 93 -



Step 4

To a solution of N'-acetyl-3-((R)-3-((S)-1-(4-bromophenyl)ethyl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)propanehydrazide (0.1 g, 0.21 mmol) in THF (2 mL) was added Burgess Reagent (75 mg, 0.315 mmol). The sealed vial was irradiated in the microwave at 100 °C for 15 min. The mixture was extracted with EtOAc (3 x 30 mL). The combined organic layer was washed with brine (50 mL), dried over Na₂SO₄, filtered, and concentrated. The residue was purified by preparative TLC to afford (R)-3-((S)-1-(4-bromophenyl)ethyl)-6-(2-(5-methyl-1,3,4-oxadiazol-2-yl)ethyl)-6-phenyl-1,3-oxazinan-2-one (58 mg, yield: 59%). ¹H NMR (CDCl₃): δ 1.49-1.51 (m, 3H), 2.23-2.26 (m, 2H), 2.30-2.33 (m, 2H), 2.42 (s, 3H), 2.43-2.45 (m, 1H), 2.49-2.54 (m, 1H), 2.87-2.91 (m, 1H), 3.06-3.09 (m, 1H), 5.61-5.63 (m, 1H), 6.76-6.78 (d, 2H), 7.20-7.22 (m, 2H), 7.26-7.33 (m, 2H), 7.35-7.37 (m, 3H).

Step 5

To a solution of (R)-3-((S)-1-(4-bromophenyl)ethyl)-6-(2-(5-methyl-1,3,4-oxadiazol-2-yl)ethyl)-6-phenyl-1,3-oxazinan-2-one (490 mg, 1.04 mmol), and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (424 mg, 1.67 mmol) in dry DMSO (20 mL) was added KOAc (326 mg, 3.33 mmol) and Pd(dppf)Cl₂ (25.3 mg, 0.031 mmol) under N₂ atmosphere. The mixture was warmed at 100 °C for 3 h. After TLC showed the starting material had disappeared, the solid was filtered off, water (50 mL) and EtOAc (50 mL) were added, and the mixture was extracted with EtOAc (3 x 50 mL). The combined organic layer was washed with brine (50 mL), dried over

Na₂SO₄, filtered, and concentrated. The residue was purified by prep TLC to afford (R)-6-(2-(5-methyl-1,3,4-oxadiazol-2-yl)ethyl)-6-phenyl-3-((S)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl)-1,3-oxazinan-2-one (0.395 g, yield:73.6%).

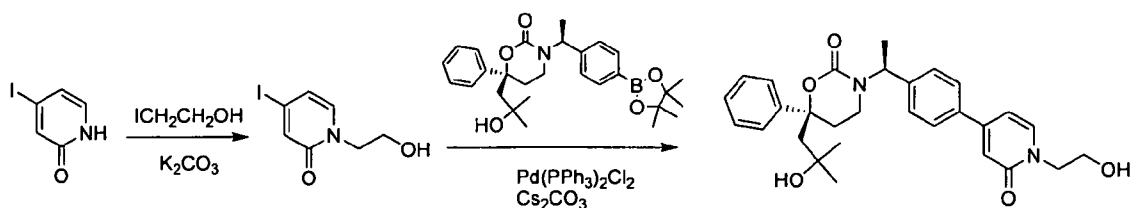
5 Step 6

To a solution of (R)-6-(2-(5-methyl-1,3,4-oxadiazol-2-yl)ethyl)-6-phenyl-3-((S)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl)-1,3-oxazinan-2-one (60 mg, 0.12 mmol) and 4-iodo-1-methylpyridin-2(1H)-one (33 mg, 0.14 mmol) in dry 1,4-dioxane (15 mL) were added Cs₂CO₃ (2M, 1 mL) and Pd(PPh₃)₂Cl₂ (7.7 mg, 0.01 mmol). The mixture was heated at reflux for 2 h under N₂ atmosphere, the solid was filtered off, and the mixture was diluted with water (30 mL) and EtOAc (30 mL). The combined organic layers was washed with brine (50 mL), dried over Na₂SO₄, filtered, and concentrated. The residue was purified by prep TLC to afford (R)-6-(2-(5-methyl-1,3,4-oxadiazol-2-yl)ethyl)-3-((S)-1-(4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)phenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one (25 mg, yield: 41.8%). LC-MS Method 2 t_R = 0.984 min, m/z = 499.1; ¹H NMR (CDCl₃): δ1.48-1.50 (m, 3H), 2.16-2.20 (m, 1H), 2.23-2.26 (m, 1H), 2.27-2.32 (m, 2H), 2.39 (s, 3H), 2.40-2.47 (m, 1H), 2.49-2.54 (m, 1H), 2.87-2.90 (m, 1H), 2.98-3.01 (m, 1H), 3.58 (s, 3H), 5.62-5.64 (m, 1H), 6.45-6.48 (m, 1H), 6.87 (s, 1H), 6.92-6.94 (d, 2H), 7.20-7.24 (m, 4H), 7.25-7.35 (m, 4H).

20

EXAMPLE 20

(S)-6-(2-hydroxy-2-methylpropyl)-3-((S)-1-(4-(1-(2-hydroxyethyl)-2-oxo-1,2-dihydropyridin-4-yl)phenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one



25

Step 1

To the mixture of 4-iodopyridin-2(1H)-one (50 mg, 0.213 mmol) in DMF (3mL) was added 2-iodoethanol (73 mg, 0.426mmol), K₂CO₃ (88 mg, 0.638 mmol) at rt. The mixture was stirred for 2 h at rt. After the reaction was finished, the mixture was washed with water and extracted with EtOAc. The organic phase was washed with brine, dried over Na₂SO₄, filtered, and concentrated to give the crude product, which was purified by TLC to provide 1-(2-hydroxyethyl)-4-iodopyridin-2(1H)-one (60 mg 100 %).

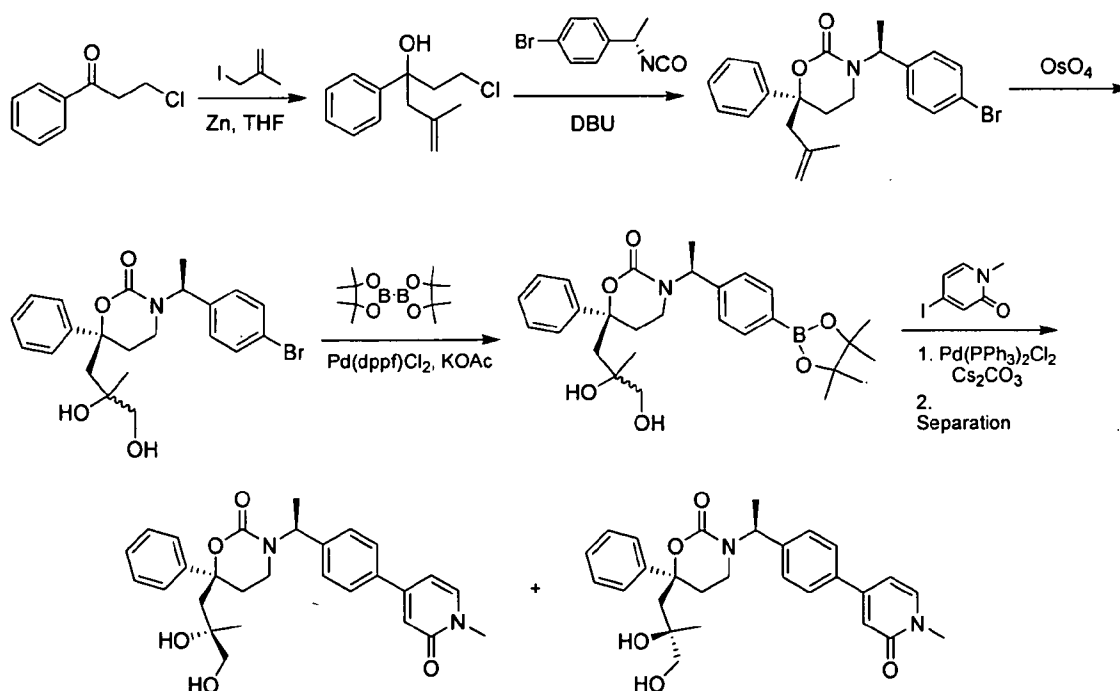
Step 2

A mixture of compounds (S)-6-(2-hydroxy-2-methylpropyl)-6-phenyl-3-((S)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl)-1,3-oxazinan-2-one (72 mg 0.150 mmol), 1-(2-hydroxyethyl)-4-iodopyridin-2(1H)-one (48 mg 0.181 mmol), Pd(PPh₃)₂Cl₂ (14 mg, 0.020 mmol), and Cs₂CO₃ (2 mL) in 1,4-dioxane (8 mL) was stirred at reflux for 2h. After the reaction was finished, the mixture was washed with water, and extracted with EtOAc. The organic phase was washed with brine, dried over Na₂SO₄, filtered, and concentrated to get the crude product, which was purified by TLC to provide compound (S)-6-(2-hydroxy-2-methylpropyl)-3-((S)-1-(4-(1-(2-hydroxyethyl)-2-oxo-1,2-dihydropyridin-4-yl)phenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one (19.7 mg, 28 %). LC-MS Method 2 t_R = 1.065 min, m/z = 491.2; ¹HNMR (CDCl₃): δ 1.10 (d, 6H), 1.50 (d, 3H), 2.20 (m, 5H), 2.35 (m, 1H), 3.50 (m, 1H), 3.90 (m, 2H), 4.10 (m, 2H), 5.60 (m, 1H), 6.40 (m, 1H), 6.70 (s, 1H), 6.95 (d, 2H), 7.35 (m, 8H).

15

EXAMPLE 21

(6S)-6-(2,3-dihydroxy-2-methylpropyl)-3-((S)-1-(4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)phenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one



20

Step 1

A solution of 3-chloro-1-phenylpropan-1-one (16.8 g, 0.1 mol) in THF (50 mL) was added to a well-stirred suspension of zinc powder (13 g, 0.2 mol) in a mixture of satd aq NH₄Cl solution (260 mL) and THF (65 mL). A solution of 3-iodo-2-methylprop-1-ene (36.4 g, 0.2 mol) in THF (50 mL) was added dropwise. The reaction was mildly exothermic, and the mixture began to reflux spontaneously. After refluxing had ceased, the mixture was stirred for 1 h. TLC showed the 3-chloro-1-phenylpropan-1-one had not reacted completely. A solution of 3-iodo-2-methylprop-1-ene (18.2 g, 0.1 mol) in THF (30 mL) was added, and the mixture was stirred at rt overnight. The mixture was extracted with EtOAc (2 x 500 mL). The combined organic layer was dried and concentrated. The residue was purified by column chromatography on silica gel eluted with petroleum ether/ EtOAc 50:1→30:1→5:1, to give 1-chloro-5-methyl-3-phenylhex-5-en-3-ol (17 g, yield 76 %) as an oil. ¹H NMR (CDCl₃): δ 1.28 (s, 3H), 2.31 (m, 2H), 2.54 (m, 2H), 2.68 (d, 1H), 3.15 (m, 1H), 3.58 (m, 1H), 4.78 (m, 1H), 4.93 (m, 1H), 7.27 (t, 1H), 7.38 (m, 4H).

Step 2

A mixture of 1-chloro-5-methyl-3-phenylhex-5-en-3-ol (2.9 g, 13 mmol), (S)-1-bromo-4-(1-isocyanatoethyl)benzene (3.5 g, 16 mmol), and DBU (8 g, 33 mmol) in THF (80 mL) was heated at reflux overnight. The mixture was diluted with EtOAc, and washed with 1N aq HCl. The aqueous phase was extracted with EtOAc (3 x), and the combined organic phase was dried over Na₂SO₄. After the solvents were evaporated, the crude product was purified by column chromatography to give (R)-3-((S)-1-(4-bromophenyl)-ethyl)-6-(2-methylallyl)-6-phenyl-1,3-oxazinan-2-one (1.62 g, yield: 30 %).

Step 3

To a solution of (R)-3-((S)-1-(4-bromophenyl)ethyl)-6-(2-methylallyl)-6-phenyl-1,3-oxazinan-2-one (300 mg, 0.726 mmol), 4-methylmorpholine 4-oxide (195 mg, 1.44 mmol) in a mixture of H₂O (6 mL), THF (30 mL) and *t*-BuOH (12 mL) was added osmium (VIII) oxide (4%, 0.231 mL) at 0 °C. The mixture was stirred at rt overnight. The mixture was quenched with 3% NaHSO₃ (15 mL×3) and extracted with EtOAc. The organic layer was dried over Na₂SO₄ and concentrated to give the crude product (S)-3-((S)-1-(4-bromophenyl)-ethyl)-6-(2,3-dihydroxy-2-methylpropyl)-6-phenyl-1,3-oxazinan-2-one (242 mg, 74.5%).

Step 4

To a solution of (S)-3-((S)-1-(4-bromophenyl)-ethyl)-6-(2,3-dihydroxy-2-methylpropyl)-6-phenyl-1,3-oxazinan-2-one (235 mg, 0.524 mmol) in DMSO (5 mL) were added KOAc (771.6 mg, 7.86 mmol), Pd(dppf)Cl₂ (40 mg) under N₂. The mixture was stirred at 90 °C for 3 h. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was dried over Na₂SO₄ and concentrated to give the crude product, which was purified by preparative

TLC to afford (S)-6-(2,3-dihydroxy-2-methylpropyl)-6-phenyl-3-((S)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl)-1,3-oxazinan-2-one (121 mg, 46.6%).

Step 5

5 A mixture of (S)-6-(2,3-dihydroxy-2-methylpropyl)-6-phenyl-3-((S)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl)-1,3-oxazinan-2-one (105 mg, 211.9 mmol), 4-iodo-1-methylpyridin-2(1H)-one (65 mg, 275.5 mmol), Pd(PPh₃)₂Cl₂ (20 mg) in aq. Cs₂CO₃ solution (3 mL) was stirred at reflux for 2 h. After the reaction was finished, the mixture was washed with water and extracted with EtOAc. The organic layer was dried over Na₂SO₄ and
10 concentrated to give the crude product, which was purified by preparative HPLC to afford two isomers of (6S)-6-(2,3-dihydroxy-2-methylpropyl)-3-((S)-1-(4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)phenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one

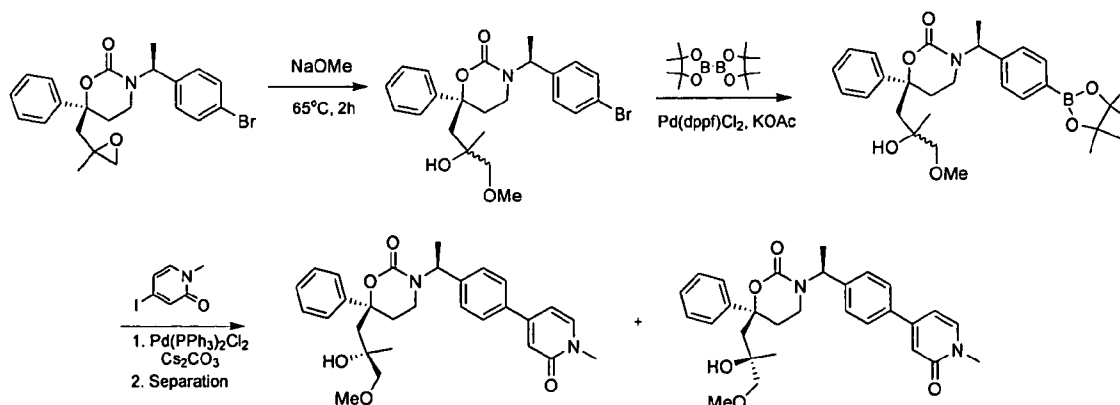
Isomer 1 (6.11 mg, 6%): LC-MS Method 2 t_R = 0.84 min, m/z = 477.4; ¹H NMR (CDCl₃):
δ 0.97 (s, 3H), 1.55 (d, 3H), 2.27 (m, 3H), 2.38 (m, 3H), 2.91 (m, 1H), 3.34 (d, 1H), 3.58 (s, 3H),
15 5.68 (m, 1H), 6.35 (d, 1H), 6.71 (s, 1H), 7.02 (d, 2H), 7.36 (m, 8H).

Isomer 2 (6.78 mg, 6.7%): LC-MS Method 2 t_R = 0.832 min, m/z = 477; ¹H NMR (CDCl₃):
δ 1.14 (s, 3H), 1.48 (d, 3H), 2.09 (m, 1H), 2.14 (m, 2H), 2.31 (m, 2H), 2.81 (m, 1H), 3.24 (d, 1H),
3.27 (d, 1H), 3.50 (s, 3H), 5.62 (m, 1H), 6.28 (d, 1H), 6.63 (s, 1H), 6.98 (d, 2H), 7.27 (m, 8H).

20

EXAMPLE 22

(6S)-6-(2-hydroxy-3-methoxy-2-methylpropyl)-3-((S)-1-(4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)phenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one



25

Step 1

Sodium (90 mg) was added to MeOH (5 mL). When sodium had disappeared, a solution of (S)-3-(S-1-(4-bromophenyl)ethyl)-6-((2-methyloxiran-2-yl)-methyl)-6-phenyl-1,3-oxazinan-2-

one (500 mg, 1.16mmol) was added to the mixture. The mixture was stirred at 65 °C for 5 h. The mixture was added H₂O and concentrated. The residue was extracted with EtOAc, the organic layer was dried over Na₂SO₄ and concentrated to give the crude product, which was purified by preparative TLC (2:1 PE/EtOAc) to afford (S)-3-(S-1-(4-bromophenyl)ethyl)-6-(2-hydroxy-3-methoxy-2-methylpropyl)-6-phenyl-1,3-oxazinan-2-one (227 mg, 42.3%).

Step 2

To a solution of (S)-3-(S-1-(4-bromophenyl)ethyl)-6-(2-hydroxy-3-methoxy-2-methylpropyl)-6-phenyl-1,3-oxazinan-2-one (205 mg, 0.443 mmol) in DMSO (5 mL) was added KOAc (435.13 mg, 4.43 mmol), Pd(dppf)Cl₂ (45 mg) under N₂. The mixture was stirred at 90°C for 3 hours. The reaction mixture was quenched by water and extracted with EtOAc. The organic layer was dried over Na₂SO₄ and concentrated to give the crude product, which was purified by preparative TLC (PE:EA=1:2) to afford (S)-6-(2-hydroxy-3-methoxy-2-methylpropyl)-6-phenyl-3-((S)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl)-1,3-oxazinan-2-one (113 mg, 50%).

Step 3

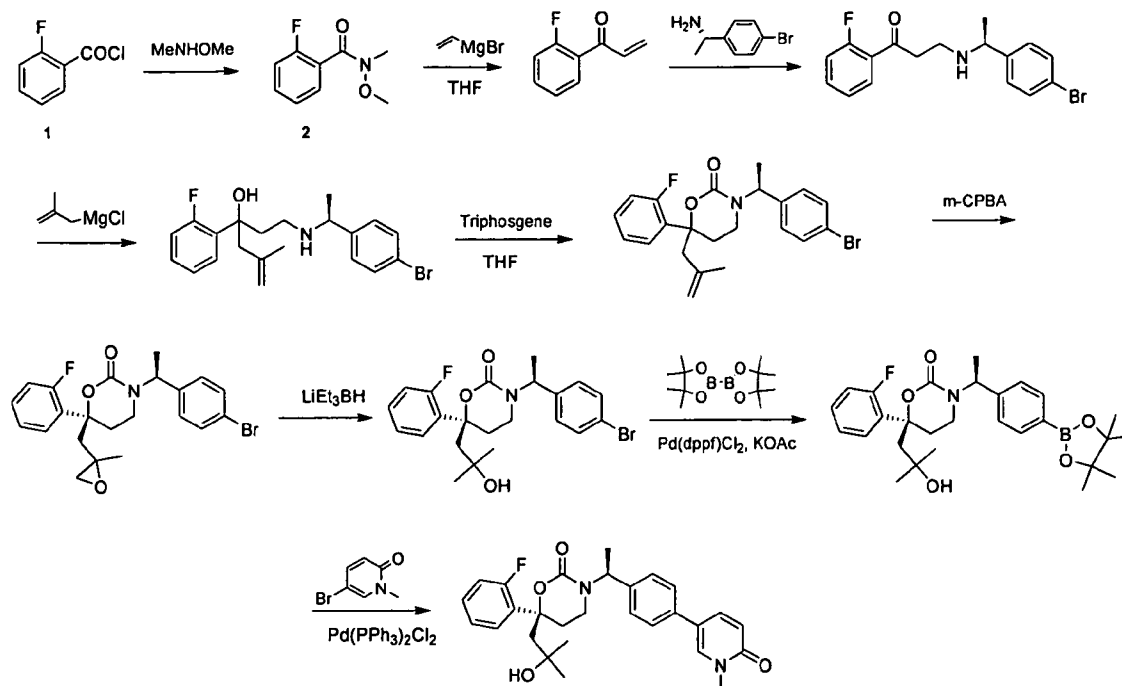
A mixture of (S)-6-(2-hydroxy-3-methoxy-2-methylpropyl)-6-phenyl-3-((S)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl)-1,3-oxazinan-2-one (100 mg, 196.29 μmol), 4-iodo-1-methylpyridin-2(1H)-one (60.49 mg, 255.2 μmol), Pd(PPh₃)₂Cl₂ (20 mg), and aq Cs₂CO₃ solution (2 mol/L, 3 mL) in 1,4-dioxane (4 mL) was stirred at reflux for 2 hours. After the reaction was finished, the mixture was washed with water and extracted with EtOAc. The organic layer was dried over Na₂SO₄ and concentrated to give the crude product, which was purified by preparative HPLC to afford two isomers of (6S)-6-(2-hydroxy-3-methoxy-2-methylpropyl)-3-((S)-1-(4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)phenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one.

Isomer 1 (5.25 mg, 5.6%): LC-MS Method 2 t_R = 0.921 min, m/z = 403.2; ¹H NMR (CDCl₃): δ 0.94 (s, 3H), 1.47 (d, 3H), 2.28 (m, 4H), 2.35 (m, 1H), 2.82 (m, 1H), 3.11 (d, 1H), 3.16 (s, 3H), 3.25 (d, 1H), 3.50 (s, 3H), 5.62 (m, 1H), 6.27 (d, 1H), 6.63 (s, 1H), 6.92 (d, 2H), 7.25 (m, 8H).

Isomer 2 (5.40 mg, 5.8%): LC-MS Method 2 t_R = 0.923 min, m/z = 513.1; ¹H NMR (CDCl₃): δ 1.18 (s, 3H), 1.47 (d, 3H), 2.11 (m, 2H), 2.23 (m, 2H), 2.45 (m, 1H), 2.81 (d, 2H), 2.96 (d, 1H), 3.15 (s, 3H), 3.50 (s, 3H), 5.62 (m, 1H), 6.27 (d, 1H), 6.65 (s, 1H), 6.90 (d, 2H), 7.26 (m, 8H).

EXAMPLE 23

(S)-6-(2-fluorophenyl)-6-(2-hydroxy-2-methylpropyl)-3-((S)-1-(4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-1,3-oxazinan-2-one



Step 1

5 To a solution of 2-fluorobenzoyl chloride (50 g, 0.31 mol) in CH_2Cl_2 (200 mL) was added *N,O*-dimethylhydroxylamine (46 g, 0.47 mol), and a solution of triethylamine (127 g, 1.26 mol) in CH_2Cl_2 (100 mL) at 0 °C. The reaction mixture was warmed slowly to rt, and stirred for 3 h. The mixture was quenched with iced water and extracted with CH_2Cl_2 (200 mL). The organic layer was dried over Na_2SO_4 , filtered, and concentrated to afford 2-fluoro-*N*-methoxy-*N*-methylbenzamide (48 g, yield: 84.6 %).

Step 2

15 A solution of 2-fluoro-*N*-methoxy-*N*-methylbenzamide (16 g, 87.4 mmol) in THF (150 mL) was cooled to -78°C. Vinylmagnesium bromide (120 mL, 120 mmol) was slowly added, and the mixture stirred at -78 °C for 10 min, slowly warmed to rt, and stirred for another 3 h. The reaction mixture was quenched with 1 N aq HCl (100 mL) at 0 °C. The aqueous layer was extracted with EtOAc (100 mL). The combined organic phase was washed with brine (50 mL), dried over Na_2SO_4 , and concentrated. The residue was purified by column chromatography to afford 1-(2-fluorophenyl)-prop-2-en-1-one (7.6 g, yield: 58.4 %) as a colorless oil.

20

Step 3

To a solution of 1-(2-fluorophenyl)-prop-2-en-1-one (5.6 g, 37.3 mmol) in CH₃CN (50 mL) was added (S)-1-(4-bromophenyl)-ethylamine (7.4 g, 37 mmol), and the mixture was stirred for 12 h at 40 °C. The solution was concentrated to afford the crude product, which was purified by column chromatography to give (S)-3-(1-(4-bromophenyl)-ethylamino)-1-(2-fluorophenyl)-propan-1-one (4 g, yield: 30.7%) as a yellow liquid.

Step 4

To a suspension of Mg (2.5 g, 104 mmol), I₂ (0.1 g) in anhydrous THF (15 mL) was added 3-chloro-2-methylprop-1-ene (0.6 mL, 6 mmol). After a solution of 3-chloro-2-methylprop-1-ene (9 mL, 90 mmol) in THF (120 mL) was dropped at 0 °C under N₂ in 30 min. (S)-3-(1-(4-bromophenyl)-ethylamino)-1-(2-fluorophenyl)-propan-1-one (3 g, 8.6 mmol) in THF (50 mL) was added dropwise at -78 °C over 45 min. The reaction mixture was stirred at rt for 2 h and cautiously quenched by addition of satd aq NH₄Cl. The mixture was extracted with EtOAc, and the organic layer was washed with brine, dried over anhydrous Na₂SO₄, and concentrated in *vacuo* to give 1-(S-1-(4-bromophenyl)-ethylamino)-3-(2-fluorophenyl)-5-methylhex-5-en-3-ol (3.3 g, yield: 94.5%), which was used for the next step without further purification.

Step 5

A mixture of 1-(S-1-(4-bromophenyl)ethylamino)-3-(2-fluorophenyl)-5-methylhex-5-en-3-ol (2 g, 5 mmol) in a solution of triethylamine (1.5 g, 15 mmol) in 1,2-dichloroethane (100 mL) was added triphosgene (1.46 g, 5 mmol) at 0 °C under N₂, and the mixture was heated at 100 °C for 4 h. The reaction mixture was quenched with water, and extracted with CH₂Cl₂ (100 mL). The combined organic layer was washed with brine, dried over Na₂SO₄, filtered, and concentrated to afford the crude product (2.1 g, yield: 99%), which was used for the next step without further purification.

Step 6

To a solution of (S)-3-(1-(4-bromophenyl)ethyl)-6-(2-fluorophenyl)-6-(2-methylallyl)-1,3-oxazinan-2-one (3.2 g, 7.4 mmol) in dry CH₂Cl₂ (100 mL) was added *m*-CPBA (2.6 g, 14.8 mmol) at rt and the mixture was stirred overnight. The mixture was diluted with (CH₃)₃COCH₃ (100 mL), washed with 30% aq Na₂S₂O₃ and aq NaHCO₃, dried over Na₂SO₄, filtered, and concentrated to give 3-(S-1-(4-bromophenyl)-ethyl)-6-(2-fluorophenyl)-6-(2-methyloxiran-2-yl-methyl)-1,3-oxazinan-2-one (2.8 g, yield: 84.3%), which was used directly for the next step without further purification.

Step 7

To a solution of 3-(S-1-(4-bromophenyl)-ethyl)-6-(2-fluorophenyl)-6-(2-methyloxiran-2-yl)-methyl-1,3-oxazinan-2-one (2.2 g, 4.92 mmol) in THF (100 mL) was added dropwise LiEt_3BH (Super-hydride, 50 mL, 50 mmol) at 0 °C under N_2 for 30 min., and the resulting mixture was stirred at 2-3°C for 1.5 h, and stirred for 2.5 h at 10-13°C. H_2O_2 (20 mL) was added dropwise and the reaction mixture was diluted with $(\text{CH}_3)_3\text{COCH}_3$ (280 mL). The mixture was washed with water, 30% aq $\text{Na}_2\text{S}_2\text{O}_3$ and brine. The organic phase was dried over Na_2SO_4 and filtered. The filtrate was concentrated to give the crude product, which was purified by column chromatography to afford (S)-3-(S-1-(4-bromophenyl)-ethyl)-6-(2-fluorophenyl)-6-(2-hydroxy-2-methylpropyl)-1,3-oxazinan-2-one (550 mg, 23.9 %) as a white solid. ^1H NMR (CDCl_3): δ 1.03 (s, 3H), 1.14 (s, 3H), 1.43 (d, J = 6.8 Hz, 3H), 2.08-2.13 (m, 1H), 2.17 (d, J = 2.8 Hz, 1H), 2.21-2.22 (m, 1H), 2.31 (dd, J = 0.8, 15.2 Hz, 1H), 2.77-2.81 (m, 1H), 5.56 (q, J = 2.8 Hz, 2 H), 6.82-6.83 (m, 2H), 6.85-6.94 (m, 1H), 7.08-7.13 (m, 1H), 7.18-7.25 (m, 1H), 7.26-7.40 (m, 2H), 7.42-7.44 (m, 1H).

Step 8

To a solution of (S)-3-(S-1-(4-bromophenyl)-ethyl)-6-(2-fluorophenyl)-6-(2-hydroxy-2-methylpropyl)-1,3-oxazinan-2-one (540 mg, 1.2 mmol) in DMSO (15 mL) was added 4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (900 mg, 3.3 mmol), $\text{CH}_3\text{CO}_2\text{K}$ (1.5 g, 16 mmol), $\text{Pd}(\text{dppf})\text{Cl}_2$ (108 mg, 0.13 mmol) under N_2 , and the reaction was stirred at 90 °C for 2.5 h. The mixture was quenched with water, and extracted with EtOAc (90 mL). The organic layer was washed with water and brine, dried over Na_2SO_4 , and filtered. The filtrate was concentrated to give the crude product, which was purified by preparative TLC to afford (S)-6-(2-fluorophenyl)-6-(2-hydroxy-2-methylpropyl)-3-((S)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl)-1,3-oxazinan-2-one (360 mg, 62 %) as a yellow liquid.

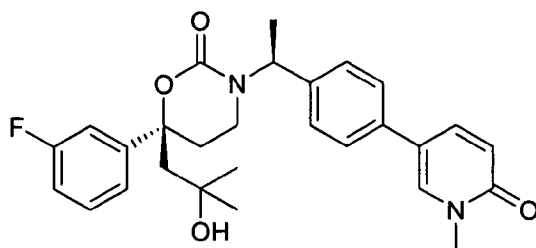
Step 9

To a solution of (S)-6-(2-fluorophenyl)-6-(2-hydroxy-2-methylpropyl)-3-((S)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl)-1,3-oxazinan-2-one (120 mg, 0.24 mmol), 5-bromo-1-methylpyridin-2-(1H)-one (54 mg, 0.28 mmol), 2N aq Cs_2CO_3 (2 mL) in dioxane (8 mL) was added $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (17 mg, 0.024 mmol) under N_2 . The reaction mixture was refluxed for 2 h and quenched by addition of water. The mixture was extracted with EtOAc (30 mL), and the organic layer was washed with H_2O and brine, dried over Na_2SO_4 , and filtered. The filtrate was concentrated to give the crude product, which was purified by preparative TLC and preparative HPLC to afford (S)-6-(2-fluorophenyl)-6-(2-hydroxy-2-methylpropyl)-3-((S)-1-(4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-1,3-oxazinan-2-one (14 mg, yield: 10 %). LC-MS Method 2 t_R = 1.2 min, m/z = 473.9; ^1H NMR (CDCl_3): δ 1.21 (s, 3H), 1.30 (s, 3H), 1.48 (d, J = 7.2 Hz, 3H), 2.15-2.26 (m, 3H), 2.33 (dd, J = 11.2, 26.4 Hz, 1H), 2.43-2.46 (m, 1H), 2.79-2.85 (m, 1H), 3.63 (s,

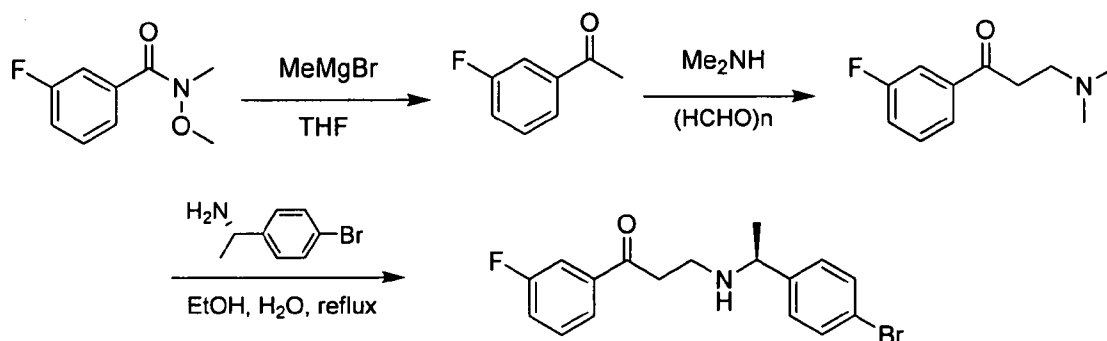
3H), 5.62 (q, $J = 6.8$ Hz, 1H), 6.58-6.60 (m, 1H), 6.89-6.94 (m, 1H), 7.00-7.02 (m, 2 H), 7.10-7.24 (m, 3H), 7.34-7.39 (m, 1H), 7.40-7.45 (m, 1H), 7.48-7.70 (m, 2H).

EXAMPLE 24

- 5 (S)-6-(3-fluorophenyl)-6-(2-hydroxy-2-methylpropyl)-3-((S)-1-(4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-1,3-oxazinan-2-one



- The title compound was prepared from (S)-3-(1-(4-bromophenyl)ethylamino)-1-(3-fluorophenyl)propan-1-one following procedures analogous to those described in Steps 4-9 in Example 23. LC-MS Method 2 $t_R = 1.416$ min, $m/z = 500.9$; ^1H NMR ($CDCl_3$) 1.18 (s, 3H), 1.29 (s, 3H), 1.47 (d, 3H), 2.05-2.28 (m, 4H), 2.31-2.39 (m, 1H), 2.82-2.87 (m, 1H), 3.58 (s, 3H), 5.64 (q, 1H), 6.57-6.59 (m, 1H), 6.88-7.19 (m, 5H), 7.21-7.25 (m, 2 H), 7.28 (m, 1H), 7.36 (m, 1H), 7.40-7.45 (m, 1H), 7.45-7.48 (m, 1H)
- 15 (S)-3-(1-(4-bromophenyl)ethylamino)-1-(3-fluorophenyl)propan-1-one was prepared as shown below.



Step 1

- 20 A solution of 3-fluoro-*N*-methoxy-*N*-methylbenzamide (16 g, 87.4 mmol) in THF (150 mL) was cooled to $-78^\circ C$. Vinylmagnesium bromide (120 mL, 120 mmol) was added slowly. The mixture was stirred at $-78^\circ C$ for 10 min, at rt for 3 h, and quenched by addition of 1 N aq HCl (100 mL) at $0^\circ C$. The aqueous layer was extracted with EtOAc (100 mL). The combined organic phase was washed with brine (50 mL), dried over Na_2SO_4 , and concentrated. The residue was

purified by column chromatography to afford 1-(3-fluorophenyl)ethanone (9.7 g, yield: 75 %) as a colorless oil.

Step 2

- 5 1-(3-Fluorophenyl)ethanone (17 g, 0.123 mol), dimethylamine (13.7 g, 0.172 mol), and paraformaldehyde (5.5 g, 0.185 mol) were suspended in ethanol (50 mL), and conc HCl solution (0.3 mL) was added. The mixture was heated at reflux overnight. The solvent was removed under vacuum, and the residue was washed with EtOAc (3 x) to give 3-(dimethylamino)-1-(3-fluorophenyl)propan-1-one (20.7 g, 88%), which was used for the next step without purification.

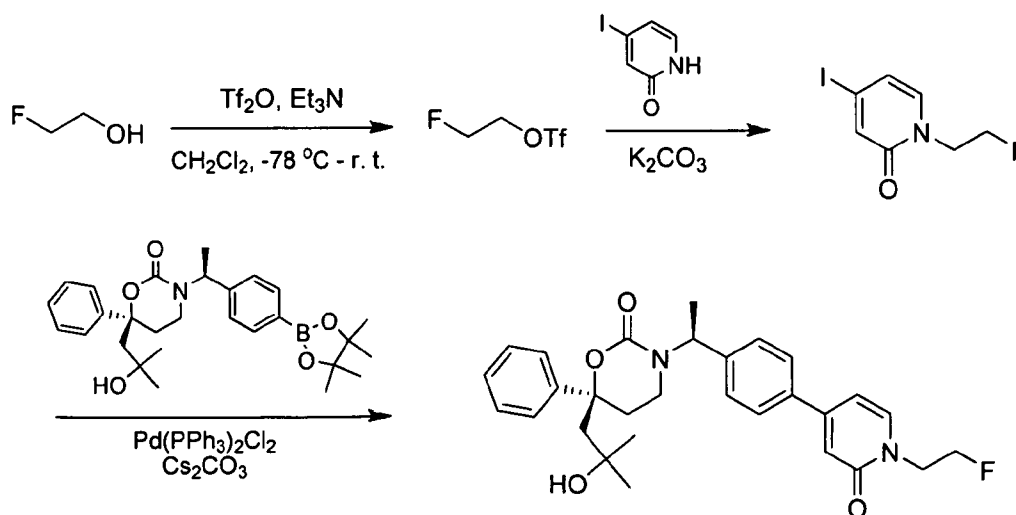
10

Step 3

- A solution of 3-dimethylamino-1-(3-fluoro-phenyl)-propan-1-one (17 g, 0.087 mol) and (S)-1-(4-bromophenyl)-ethanamine (17 g, 0.087 mol) in a mixture of EtOH (50 mL) and H₂O (50 mL) was refluxed at 80 °C overnight. The solvent was removed under vacuum, and the residue was purified by column chromatography to afford (S)-3-(1-(4-bromophenyl)-ethylamino)-1-(3-fluorophenyl)-propan-1-one (6.2 g, 20%).

EXAMPLE 25

- 20 (S)-3-((S)-1-(4-(1-(2-fluoroethyl)-2-oxo-1,2-dihydropyridin-4-yl)phenyl)ethyl)-6-(2-hydroxy-2-methylpropyl)-6-phenyl-1,3-oxazinan-2-one



- 1-(2-fluoroethyl)-4-iodopyridin-2(1H)-one was prepared from 4-iodopyridin-2(1H)-one and 2-fluoroethyl trifluoromethanesulfonate following a procedure analogous to that described in Example 20 Step 1.

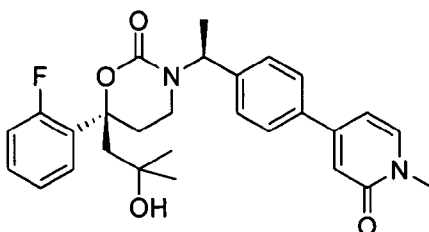
25

The title compound was prepared from (S)-6-(2-hydroxy-2-methylpropyl)-6-phenyl-3-((S)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl)-1,3-oxazinan-2-one and 1-(2-fluoroethyl)-4-iodopyridin-2(1H)-one following a procedure analogous to that described in Example 6 Step 1. LC-MS Method 2 t_R = 1.09 min, m/z = 515, 493, 475, 435.

5

EXAMPLE 26

(S)-6-(2-fluorophenyl)-6-(2-hydroxy-2-methylpropyl)-3-((S)-1-(4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)phenyl)ethyl)-1,3-oxazinan-2-one



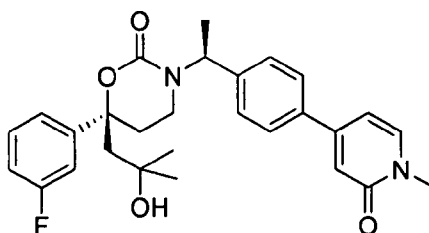
10

The title compound was prepared from (S)-6-(2-fluorophenyl)-6-(2-hydroxy-2-methylpropyl)-3-((S)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl)-1,3-oxazinan-2-one and 4-iodo-1-methylpyridin-2(1H)-one following a procedure analogous to that described in Example 23 Step 9. LC-MS Method 2 t_R = 1.58 min, m/z = 501, 479, 421.

15

EXAMPLE 27

(S)-6-(3-fluorophenyl)-6-(2-hydroxy-2-methylpropyl)-3-((S)-1-(4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)phenyl)ethyl)-1,3-oxazinan-2-one



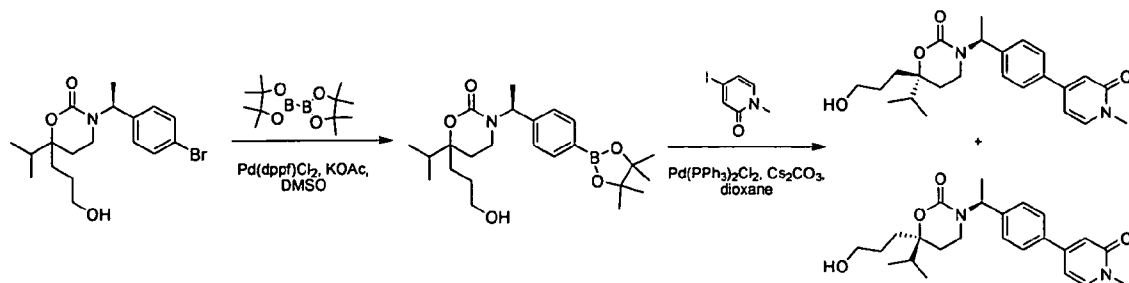
20

The title compound was prepared from (S)-6-(3-fluorophenyl)-6-(2-hydroxy-2-methylpropyl)-3-((S)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl)-1,3-oxazinan-2-one and 4-iodo-1-methylpyridin-2(1H)-one following a procedure analogous to that described in Example 23 Step 9. LC-MS Method 2 t_R = 1.57 min, m/z = 501, 479, 421.

25

EXAMPLE 28

6-(3-hydroxypropyl)-6-isopropyl-3-((S)-1-(4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)phenyl)ethyl)-1,3-oxazinan-2-one



The two diastereomers of the title compound were prepared from 3-((*S*)-1-(4-bromophenyl)ethyl)-6-(3-hydroxypropyl)-6-isopropyl-1,3-oxazinan-2-one following procedures analogous to those described in Example 23 Steps 8 and 9.

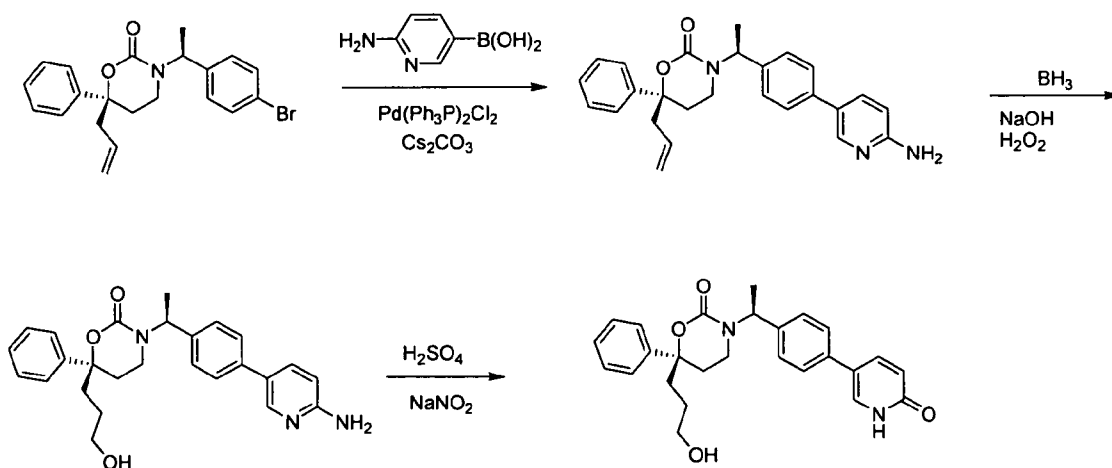
Isomer 1: LC-MS Method 2 t_R = 1.06 min, m/z = 413.

Isomer 2: LC-MS Method 2 t_R = 1.03 min, m/z = 413.

EXAMPLE 29

4108.1002-007 EXAMPLE 221]

(*R*)-6-(3-hydroxypropyl)-3-((*S*)-1-(4-(6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one



Step 1

A mixture of (*R*)-6-allyl-3-((*S*)-1-(4-bromophenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one (150 mg, 0.375 mmol) and 6-aminopyridin-3-ylboronic acid (56 mg, 0.45 mmol), Pd(PPh₃)₂Cl₂ (15 mg), and aqueous Cs₂CO₃ solution (0.5 mL, 2 M) in 1,4-dioxane (10 mL) was stirred and heated to reflux for 2 h. The organic phase was separated, and concentrated to give the crude product,

which was purified by preparative HPLC to give (*R*)-6-allyl-3-((*S*)-1-(4-(6-aminopyridin-3-yl)phenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one (90 mg, 60%).

Step 2

- 5 To a solution of (*R*)-6-allyl-3-((*S*)-1-(4-(6-aminopyridin-3-yl)phenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one (90 mg, 0.23 mmol) in tetrahydrofuran (10 mL) was added BH₃ THF (3.0 mL, 1 mol/L, 4 mmol) at 0 °C under nitrogen atmosphere. The formed mixture was stirred for 2 h. The reaction was quenched by water. Then NaOH (2 mL, 3 mol/L) and H₂O₂ (1 mL) was added to the above mixture. When the reaction was over, the mixture was extracted with EtOAc. The combined organic phase was concentrated to give the crude product, which was purified by preparative HPLC to give (*R*)-3-((*S*)-1-(4-(6-aminopyridin-3-yl)phenyl)ethyl)-6-3-hydroxypropyl)-6-phenyl-1,3-oxazinan-2-one (40 mg, 41%).

Step 3

- 15 (*R*)-3-((*S*)-1-(4-(6-aminopyridin-3-yl)phenyl)ethyl)-6-(3-hydroxypropyl)-6-phenyl-1,3-oxazinan-2-one (40 mg, 0.09 mmol) was dissolved in 3.5 M H₂SO₄ (10 mL), and 2 M NaNO₂ (10 mL) was added at 0 °C. The reaction mixture was stirred at rt for 2 h and treated with NaOH solution. The mixture was extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na₂SO₄, and concentrated to afford the residue, which was purified by preparative HPLC to give (*R*)-6-(3-hydroxypropyl)-3-((*S*)-1-(4-(6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one (10 mg, 20%). LC-MS Method 2 *t*_R = 1.66, min, *m/z* = 433, 455; ¹H NMR (CDCl₃): 1.36 (m, 2H), 1.50 (m, 3H), 1.68 (m, 2H), 1.92 (m, 2H), 2.10-2.30 (m, 3H), 2.84 (m, 1H), 3.50 (m, 2H), 5.12 (m, 1H), 6.62 (m, 1H), 6.86 (m, 2H), 7.08 (m, 2H), 7.18-7.32 (m, 5H), 7.46 (m, 1H), 7.62 (m, 1H).

25

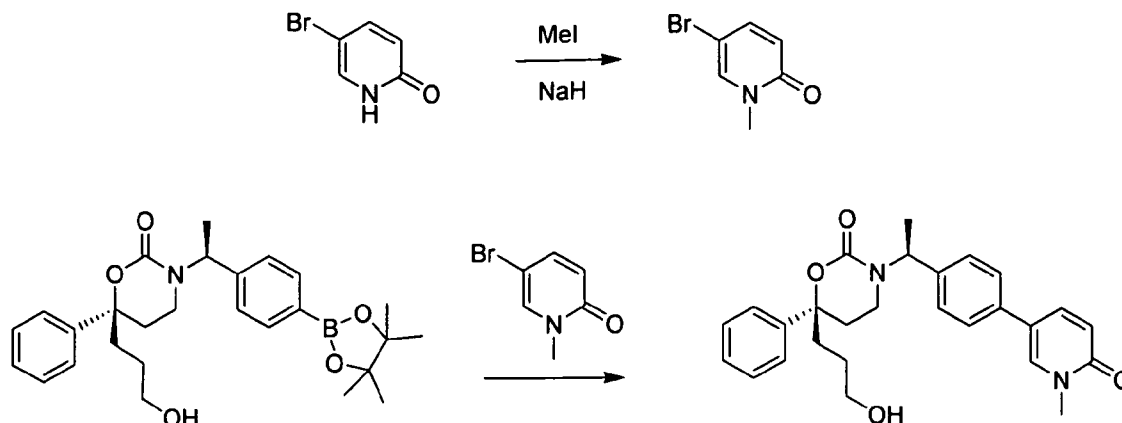
EXAMPLE 30

4108.1002-007 EXAMPLE 313

(*R*)-6-(3-hydroxypropyl)-3-((*S*)-1-(4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one

30

- 107 -



Step 1

To a suspension of NaH (4.8 g, 0.2 mol) in THF (10 mL) was added a solution of 5-bromopyridin-2(1H)-one (8.6 g, 0.05 mol) in THF (120 mL) at 0 °C. The resulting mixture was stirred for 1 h and CH₃I (35.5 g, 0.25 mol) was added. The mixture was stirred for 3 h. The reaction was quenched with aqueous NH₄Cl solution. The organic phase was concentrated to give the crude product, which was purified by column chromatography to give 5-bromo-1-methylpyridin-2(1H)-one (8.9 g, 96.78 %). ¹H NMR (CDCl₃): δ= 3.5 (s, 3H), 6.52 (m, 1H), 7.32 (m, 1H), 7.45 (m, 1H).

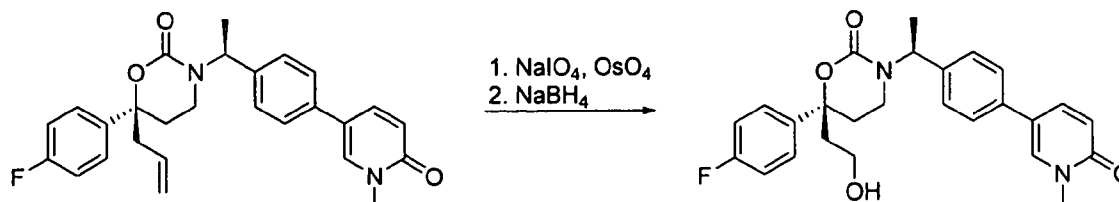
Step 2

A mixture of (*R*)-6-(3-hydroxypropyl)-6-phenyl-3-((*S*)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl)-1,3-oxazinan-2-one (1.7 g, 3.7 mmol) and 5-bromo-1-methylpyridin-2(1H)-one (816 mg, 4.4 mmol), Pd(Ph₃P)₂Cl₂ (200mg), and aq Cs₂CO₃ solution (4mL, 2M) in 1,4-dioxane (30 mL) was stirred and heated to reflux for 2 h. When the reaction was over, the mixture was washed with water and extracted with EtOAc, and the organic phase was washed with brine, dried over Na₂SO₄, filtered and concentrated to give crude product, which was purified by preparative TLC to give (*R*)-6-(3-hydroxypropyl)-3-((*S*)-1-(4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one (614 mg, 37%). LC-MS Method 2 t_R = 1.075 min, m/z = 447.1; ¹H NMR (CDCl₃): δ=1.38 (m, 1H), 1.47 (d, 3H), 1.73 (m, 2H), 1.98 (m, 2H), 2.20 (m, 1H), 2.31 (m, 2H), 2.94 (m, 1H), 3.51 (m, 2H), 3.56 (s, 3H), 5.63 (m, 1H), 6.67 (m, 1H), 6.87 (m, 2H), 7.05 (m, 2H), 7.31-7.41 (m, 6H), 7.48 (m, 1H).

EXAMPLE 31

4108.1002-007 EXAMPLE458]

(*S*)-6-(4-fluorophenyl)-6-(2-hydroxyethyl)-3-((*S*)-1-(4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-1,3-oxazinan-2-one



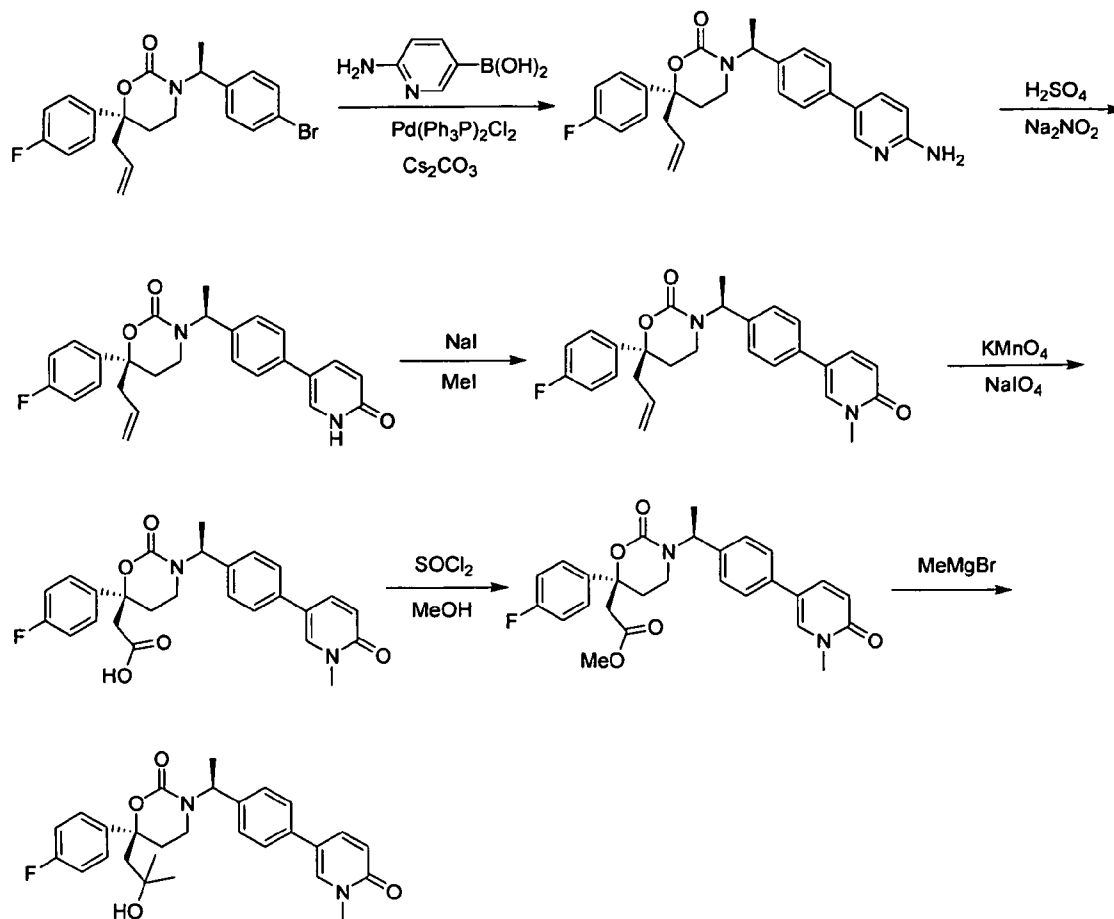
To a solution of (R)-6-allyl-6-(4-fluorophenyl)-3-((S)-1-(4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-1,3-oxazinan-2-one (0.064 g, 0.144 mmol, 1.0 equiv) in THF-H₂O (1:1, 6 mL) were added NaIO₄ (0.145 g, 0.678 mmol, 4.7 equiv) and OsO₄ (2.5 wt. % solution in *t*-BuOH, 0.048 g, 0.0047 mmol, 0.033 equiv), and the mixture was stirred at rt for 1 h. The mixture was diluted with EtOAc, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was dissolved in MeOH (3 mL) and NaBH₄ (0.100 g) was added. After the mixture was stirred for 0.5 h at rt, acetone was added. The solvents were removed in vacuo, the residue was treated with saturated brine, extracted with CH₂Cl₂, and dried over Na₂SO₄. After the solvent was evaporated, the residue was purified by reversed-phase HPLC (SunFire™ Prep C₁₈ OBD™ 5 μm 19 × 50 mm column, 10% → 90% CH₃CN/H₂O, 0.1% CF₃COOH over 8 min and then 90% CH₃CN/H₂O, 0.1% CF₃COOH over 2 min, flow rate 20 mL/min) to afford (S)-6-(4-fluorophenyl)-6-(2-hydroxyethyl)-3-((S)-1-(4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-1,3-oxazinan-2-one. LC-MS Method 1 *t_R* = 1.21 min, *m/z* = 451 (*M*+1); ¹H NMR (400 MHz, CD₃OD) δ 7.80 (m, 1H), 7.69 (d, *J* = 9.4 Hz, 1H), 7.22-7.19 (m, 4H), 7.00-6.92 (m, 4H), 6.52 (d, *J* = 9.4 Hz, 1H), 5.45 (q, *J* = 7.0 Hz, 1H), 3.60-3.52 (m, 1H), 3.52 (s, 3H), 3.24-3.18 (m, 1H), 3.02-2.98 (m, 1H), 2.39-2.35 (m, 1H), 2.23-2.12 (m, 2H), 2.01 (t, *J* = 7.3 Hz, 2H), 1.43 (d, *J* = 7.0 Hz, 3H); ¹⁹F NMR (376 MHz, CD₃OD) δ -117.19 (m).

EXAMPLE 32

4108.1002-007 EXAMPLE 459]

(S)-6-(4-fluorophenyl)-6-(2-hydroxy-2-methylpropyl)-3-((S)-1-(4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-1,3-oxazinan-2-one

Method 1



Step 1

A mixture of (*R*)-6-allyl-3-((*S*)-1-(4-bromophenyl)ethyl)-6-(4-fluorophenyl)-1,3-oxa zinan- 2-
 5 one (1.6 g, 3.84 mmol) and 6-aminopyridin-3-ylboronic acid (1.0 g, 4.61 mmol), Pd(Ph₃P)₂Cl₂ (150 mg), and aq Cs₂CO₃ solution (3.84 mL, 2 M) in 1,4-dioxane (150 mL) was stirred and heated to reflux for 2 h. The mixture was filtered and the filtrate was extracted with EtOAc. The combined organic phase was washed with brine, dried over anhydrous Na₂SO₄, and concentrated to give (*R*)-6-allyl-3-((*S*)-1-(4- (6-aminopyridin -3-yl) phenyl)ethyl)-6-(4-fluorophenyl)-1,3-
 10 oxazinan-2-one (1.5 g, 90%), which was used for the next step without purification. ¹H NMR (CDCl₃): δ=1.51 (d, 3H), 2.17-2.31 (m, 3H), 2.54-2.60 (m, 2H), 2.90 (m, 1H), 4.46 (s, 2H), 4.99-5.09 (m, 2H), 5.65-5.71 (m, 2H), 6.54 (m, 2H), 6.88 (d, 2H), 7.03 (t, 2H), 7.21-7.27 (m, 3H), 7.58 (d, 1H), 8.22 (d, 1H).

Step 2

To a solution of (*R*)-6-allyl-3-((*S*)-1-(4-(6-aminopyridin-3-yl)phenyl)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one (1.5 g, 3.47 mmol) in 3.5 M H₂SO₄ (25 mL) was added 2 M

NaNO₂ (15 mL) at 0 °C. The reaction mixture was stirred at rt overnight. The reaction was treated with aqueous NaOH solution (8%), and the mixture was extracted with CH₂Cl₂. The combined organic layer was washed with brine, dried over anhydrous Na₂SO₄ and concentrated to give crude product, which was purified by preparative TLC to give (*R*)-6-allyl-6-(4-

5 fluorophenyl)-3-((*S*)-1-(4-(6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-1,3-oxazinan-2-one (891 mg, 59%). ¹H NMR (CDCl₃): δ=1.52 (d, 3H), 2.15-2.38 (m, 3H), 2.51-2.60 (m, 2H), 2.94 (m, 1H), 4.99-5.11 (m, 2H), 5.65-5.74 (m, 2H), 6.67 (m, 1H), 6.89 (d, 2H), 7.00 (t, 2H), 7.13-7.20 (m, 2H), 7.20-7.27 (d, 2H), 7.33 (m, 1H), 7.46 (m, 1H), 7.77 (m, 1H).

10 Step 3

To a suspension of NaH (330 mg, 8.24 mmol) in THF (20 mL) was added a solution of (*R*)-6-allyl-6-(4-fluorophenyl)-3-((*S*)-1-(4-(6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-1,3-oxazinan-2-one (891 mg, 0.174mmol) in THF (30 mL) at 0 °C, and the resulting mixture was stirred for 1h. CH₃I (2 ml) was added and the mixture was stirred overnight. The reaction was quenched by
15 aqueous NH₄Cl solution. The organic phase was separated, and concentrated to give the crude product, which was purified by preparative TLC to give (*R*)-6-allyl-6-(4-fluorophenyl)-3-((*S*)-1-(4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-1,3-oxazinan-2-one (634 mg, 69%). ¹H
NMR (CDCl₃): δ=1.52 (d, 3H), 2.16-2.35 (m, 3H), 2.52-2.64 (m, 2H), 2.94 (m, 1H), 3.61 (s, 3H),
20 5.00-5.11 (m, 2H), 5.66-5.74 (m, 2H), 6.64 (d, 1H), 6.90 (d, 2H), 7.02 (t, 2H), 7.11-7.14 (d, 2H), 7.25-7.28 (m, 2H), 7.41 (m, 1H), 7.53 (m, 1H).

Step 4

To a solution of (*R*)-6-allyl-6-(4-fluorophenyl)-3-((*S*)-1-(4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-1,3-oxazinan-2-one (320 mg, 0.717mmol) in acetone (20 mL)
25 was added aqueous KMnO₄ and NaIO₄ solution (15 mL). Then the formed mixture was stirred for 30 min at 0 °C. The mixture was filtered, and the filtrate was adjusted to pH = 5-6 with 1 N aq HCl solution. The mixture was extracted with EtOAc, and the combined organic phase was washed with brine, dried over anhydrous Na₂SO₄ and concentrated to give 2-((*S*)-6-(4-fluorophenyl)-3-((*S*)-1-(4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-2-oxo-1,3-oxazinan-6-yl)acetic acid.
30

Step 5

To a solution of 2-((*S*)-6-(4-fluorophenyl)-3-((*S*)-1-(4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-2-oxo-1,3-oxazinan-6-yl)acetic acid (290 mg, 0.625 mol) in MeOH (20 mL) was
35 added SOCl₂ (2 mL) at 0 °C, and the reaction mixture was stirred at rt for 2 h. The reaction mixture was concentrated to give the residue, which was purified by preparative TLC to give

methyl 2-((S)-6-(4-fluorophenyl)-3-((S)-1-(4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-2-oxo-1,3-oxazinan-6-yl)acetate (130 mg, 43.5%). ¹H NMR (CDCl₃): δ=1.52 (d, 3H), 2.36-2.55 (m, 3H), 2.67-2.71 (m, 2H), 2.90-3.04 (m, 3H), 3.68 (s, 3H), 3.71 (s, 3H), 5.66 (m, 2H), 6.66 (d, 1H), 6.90 (d, 2H), 7.03 (t, 2H), 7.13-7.15 (d, 2H), 7.23-7.29 (m, 2H), 7.42 (m, 1H), 7.56 (m, 1H).

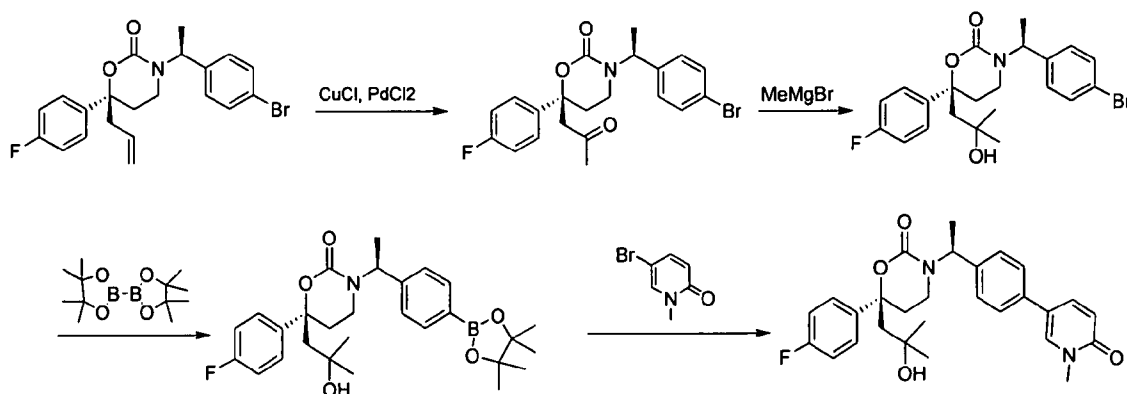
5

Step 6

To a solution of methyl 2-((S)-6-(4-fluorophenyl)-3-((S)-1-(4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-2-oxo-1,3-oxazinan-6-yl)acetate (130 mg, 0.22 mmol) in dry THF (20 mL) was added MeMgBr (2 mL) at -78 °C, and the mixture was stirred under N₂ at rt overnight. The reaction was quenched with water, and the mixture was extracted with EtOAc. The combined organic phase was dried over Na₂SO₄, and concentrated to give the residue, which was purified by preparative HPLC to give (S)-6-(4-fluorophenyl)-6-(2-hydroxy-2-methylpropyl)-3-((S)-1-(4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-1,3-oxazinan-2-one (24 mg, 30%). LC-MS Method 2 t_R = 1.116 min, m/z = 479.1; ¹H NMR (CDCl₃): 1.1 (m, 6H), 1.18 (m, 1H), 1.48 (d, 3H), 1.58 (m, 1H), 1.80-2.00 (m, 2H), 2.21 (m, 3H), 2.86 (m, 1H), 5.55 (m, 1H), 7.72 (m, 2H), 7.00 (m, 2H), 7.18 (m, 4H).

15

Method 2



20

Step 1

To a solution of (R)-6-allyl-3-((S)-1-(4-bromophenyl)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one (5 g, 12 mmol) and CuCl (2.75 g, 27.8 mmol) in dry DMF (50 mL) was added H₂O (20 mL) and PdCl₂ (950 mg, 3.2 mmol) at room temperature. The mixture was vigorously stirred under a balloon of oxygen for 24 h. After TLC showed the starting material had disappeared, the solid was filtered off. Water (200 mL) and EtOAc (50 mL) was added, the layers were separated and the aqueous layer was extracted with EtOAc (3 × 40 mL). The combined organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated to give (S)-3-((S)-1-(4-bromophenyl)ethyl)-6-(4-fluorophenyl)-6-(2-oxopropyl)-1,3-oxazinan-2-one (5.25 g, 92%), which

25

was purified by column chromatography. ^1H NMR (CDCl_3): 1.47 (s, 3H), 2.06 (s, 3H), 2.10-2.36 (m, 3H), 2.58 (m, 1H), 2.90 (m, 2H), 5.58 (m, 1H), 6.69 (m, 1H), 6.79 (m, 1H), 7.02 (m, 2H), 7.19-7.33 (m, 4H).

5 Step 2

To a solution of (S)-3-((S)-1-(4-bromophenyl)ethyl)-6-(4-fluorophenyl)-6-(2-oxopropyl)-1,3-oxazinan-2-one (5.25 g, 12.1 mmol) in anhydrous THF (100 mL) was added dropwise methylmagnesium bromide (20 mL, 60 mmol) at -78°C under nitrogen. Then the mixture was stirred at rt for 2 h. The reaction mixture was cooled in an ice bath and quenched with aqueous
 10 NH_4Cl . The layers were separated. The aqueous layer was extracted with EtOAc (15 mL), washed with a brine (30 mL), dried over Na_2SO_4 and concentrated in *vacuo* to give the crude product, which was purified by preparative HPLC and chiral HPLC to afford (S)-3-((S)-1-(4-bromophenyl)ethyl)-6-(4-fluorophenyl)-6-(2-hydroxy-2-methylpropyl)-1,3-oxazinan-2-one (2.5 mg, 46%). ^1H NMR (CDCl_3): 1.08 (s, 3H), 1.12 (s, 3H), 1.48 (m, 3H), 1.99 (m, 1H), 2.10-2.24 (m, 4H),
 15 2.35 (m, 1H), 2.85 (m, 1H), 5.61 (m, 1H), 6.80 (m, 2H), 6.99 (m, 2H), 7.15-7.28 (m, 5H).

Step 3

A mixture of (S)-3-((S)-1-(4-bromophenyl)ethyl)-6-(4-fluorophenyl)-6-(2-hydroxy-2-methylpropyl)-1,3-oxazinan-2-one (640 mg, 1.42 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-
 20 bi(1,3,2-dioxaborolane) (470 mg, 1.85 mmol), PdCl_2dppf (40 mg, 0.047 mmol), KOAc (490 mg, 4.97 mmol) in DMSO (8 mL) was heated at 90°C for 20 h. The mixture was diluted with EtOAc, and washed with water. The organic phase was separated, and concentrated to give the crude product, which was purified by preparative TLC to afford (S)-6-(4-fluorophenyl)-6-(2-hydroxy-2-methylpropyl)-3-((S)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl)-1,3-
 25 oxazinan-2-one (700 mg, 99%). ^1H NMR (CDCl_3): δ =1.08 (s, 3H), 1.13 (s, 3H), 1.32 (s, 12H), 1.51 (t, 3H), 1.94 (m, 2H), 2.16 (m, 5H), 2.33 (m, 1H), 2.83 (m, 1H), 5.69 (m, 1H), 6.99 (m, 4H), 7.25 (m, 2H), 7.61 (m, 2H).

Step 4

A mixture of (S)-6-(4-fluorophenyl)-6-(2-hydroxy-2-methylpropyl)-3-((S)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl)-1,3-oxazinan-2-one (700 mg, 1.41 mmol), 5-bromo-1-methylpyridin-2(1H)-one (398 mg, 2.12 mmol), $\text{PdCl}_2(\text{Ph}_3\text{P})_2$ (70 mg), Cs_2CO_3 (1.5 mL, 3.0 mmol) in 1,4-dioxane (15 mL) was heated under reflux for 2 h. The mixture was diluted with EtOAc, and washed with water. The organic phase was separated, and concentrated to give the
 35 crude product, which was purified by preparative TLC to afford (S)-6-(4-fluorophenyl)-6-(2-hydroxy-2-methylpropyl)-3-((S)-1-(4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-1,3-

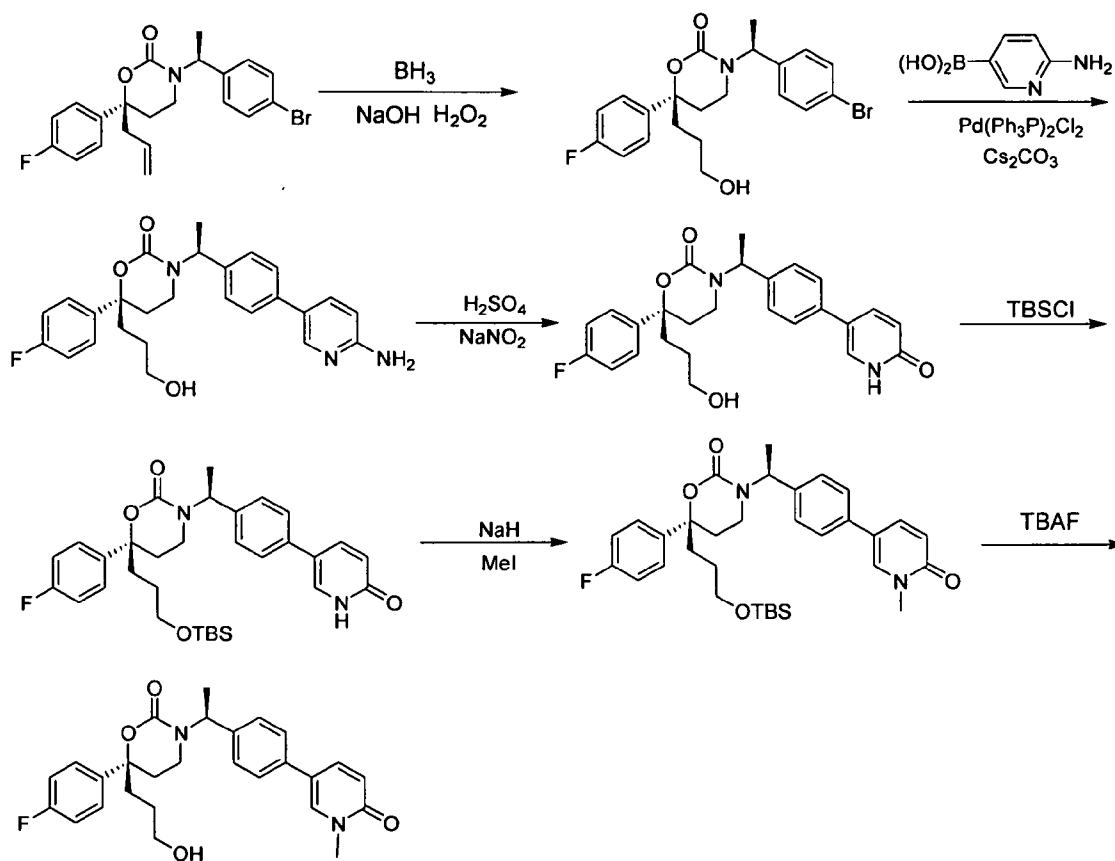
oxazinan-2-one (150 mg, 22%). ^1H NMR (CDCl_3): δ =1.12 (s, 3H), 1.13 (s, 3H), 1.51 (t, 3H), 2.16 (m, 2H), 2.21 (m, 2H), 2.41 (m, 1H), 2.92 (m, 1H), 3.63 (s, 3H), 5.69 (q, 1H), 6.69 (m, 1H), 6.99 (m, 4H), 7.18 (m, 2H), 7.27 (m, 2H), 7.42 (m, 1H), 7.52 (m, 1H).

5

EXAMPLE 33

4108.1002-007 EXAMPLE 460

(R)-6-(4-fluorophenyl)-6-(3-hydroxypropyl)-3-((S)-1-(4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-1,3-oxazinan-2-one



10

Step 1

To a solution of (R)-6-allyl-3-((S)-1-(4-bromophenyl)ethyl)-6-(4-fluorophenyl)-1,3-oxazinan-2-one (1.19g, 2.8mmol) in THF (30 mL) was added BH_3 THF (8.5 mL, 1 mol/L, 8.5mmol) at 0 °C under nitrogen atmosphere. The formed mixture was stirred for 2 h. The reaction was quenched with water. Then NaOH (1 mol/L, 6mL) and H_2O_2 (5 mL) were added to the above mixture. When the reaction was over, the mixture was extracted with EtOAc. The combined organic phase was concentrated to give the crude product, which was purified by preparative TLC to give

15

(*R*)-3-((*S*)-1-(4-bromophenyl)ethyl)-6-(4-fluorophenyl)-6-(3-hydroxypropyl)-1,3-oxazinan-2-one (1.13 g, 92%).

Step 2

- 5 A mixture of (*R*)-3-((*S*)-1-(4-bromophenyl)ethyl)-6-(4-fluorophenyl)-6-(3-hydroxypropyl)-1,3-oxazinan-2-one (520mg, 1.2mmol) and 6-aminopyridin-3-ylboronic acid (280mg, 1.44mmol), Pd(Ph₃P)₂Cl₂ (100mg), and aq Cs₂CO₃ solution (3mL, 2M) in 1,4-dioxane (20 mL) was stirred and heated to reflux for 2 h. The organic phase was separated, and concentrated to give crude product, which was purified by preparative TLC to give (*R*)-3-((*S*)-1-(4-(6-aminopyridin-3-yl)phenyl)ethyl)-6-(4-fluorophenyl)-6-(3-hydroxypropyl)-1,3-oxazinan-2-one (400mg, 74%).
- 10

Step 3

- (*R*)-3-((*S*)-1-(4-(6-aminopyridin-3-yl)phenyl)ethyl)-6-(4-fluorophenyl)-6-(3-hydroxypropyl)-1,3-oxazinan-2-one (400 mg, 0.88 mmol) was dissolved in 3.5 M H₂SO₄ (10 mL), and 2 M NaNO₂ (6 mL) was added at 0 °C. The reaction mixture was stirred at rt for 20 min. The reaction mixture was then treated with aqueous NaOH solution (8%), and extracted with CH₂Cl₂. The combined organic layer was washed with brine, dried over anhydrous Na₂SO₄, and concentrated to give crude product, which was purified by preparative TLC to give (*R*)-6-(4-fluorophenyl)-6-(3-hydroxypropyl)-3-((*S*)-1-(4-(6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-1,3-oxazinan-2-one (350 mg, 0.78 mmol). ¹H NMR (CDCl₃): δ=1.10-1.25 (m, 8H), 1.37 (m, 1H), 1.42-1.55 (m, 2H), 1.78-1.93 (m, 2H), 2.10-2.38 (m, 2H), 2.87 (m, 2H), 3.52-3.58 (m, 1H), 3.31-3.97 (m, 1H), 4.12-4.19 (m, 1H), 5.53-5.63 (m, 1H), 6.85-7.15 (m, 3H), 7.35-7.55 (m, 1H), 7.75-7.89 (m, 1H), 8.10-8.12 (m, 1H).
- 15
- 20

Step 4

- 25 A mixture of (*R*)-6-(4-fluorophenyl)-6-(3-hydroxypropyl)-3-((*S*)-1-(4-(6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-1,3-oxazinan-2-one (100 mg, 0.78 mmol), imidazole (142.8 mg, 2.1 mmol), and *tert*-butylchlorodimethylsilane (350 mg, 2.34 mmol) in CH₂Cl₂ (20 mL) was stirred overnight. The mixture was washed with water and extracted with EtOAc. The combined organic phase was washed with brine, dried over Na₂SO₄, filtered and concentrated to give crude (*R*)-6-(3-(*tert*-butyldimethylsilyloxy)propyl)-6-(4-fluorophenyl)-3-((*S*)-1-(4-(6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-1,3-oxazinan-2-one (120 mg), which was used for the next step without further purification.
- 30

Step 5

- To a suspension of NaH (18 mg, 0.72 mmol) in THF (0.5 mL) was added a solution of (*R*)-6-(3-(*tert*-butyldimethylsilyloxy)propyl)-6-(4-fluorophenyl)-3-((*S*)-1-(4-(6-oxo-1,6-dihydropyridin-3-
- 35

yl)phenyl)ethyl)-1,3-oxazinan-2-one (100mg, 0.18 mmol) in THF (10 mL) at 0 °C. The resulting mixture was stirred for 1 h. Then CH₃I (613 mg, 43.2 mmol) was added, and the mixture was stirred for 3 h. The reaction was quenched with aq NH₄Cl solution. The organic phase was separated, and concentrated to give (R)-6-(3-(tert-butyldimethylsilyloxy)propyl)-6-(4-fluorophenyl)-3-((S)-1-(4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-1,3-oxazinan-2-one (104 mg, 100%), which was used for the next step without further purification.

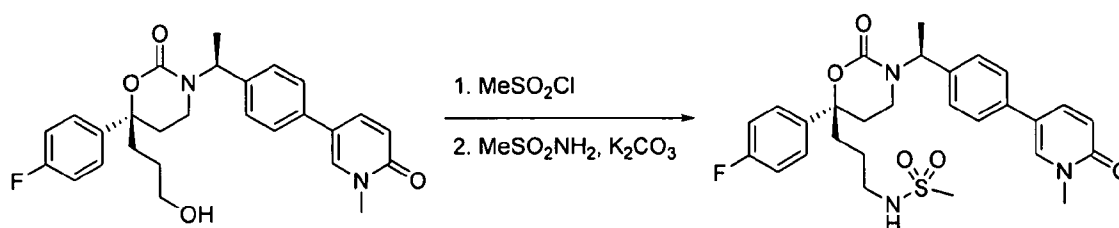
Step 6

A mixture of (R)-6-(3-(tert-butyldimethylsilyloxy)propyl)-6-(4-fluorophenyl)-3-((S)-1-(4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-1,3-oxazinan-2-one (200 mg, 0.35 mmol) and TBAF (182 mg, 0.7 mmol) in CH₃CN was stirred and heated to reflux for 15 min. When the reaction was over, the mixture was washed with water and extracted with EtOAc. The combined organic phase was washed with brine, dried over Na₂SO₄, filtered and concentrated to give crude product, which was purified by preparative HPLC to give (R)-6-(4-fluorophenyl)-6-(3-hydroxypropyl)-3-((S)-1-(4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-1,3-oxazinan-2-one (5.01 mg, 4%). LC-MS Method 2 t_R = 1.065 min, m/z = 464.21; ¹H NMR (CDCl₃): δ=1.38 (m, 1H), 1.47 (d, 3H), 1.63 (m, 2H), 1.91 (m, 2H), 2.10-2.30 (m, 3H), 2.87 (m, 1H), 2.84 (m, 1H), 3.51 (m, 2H), 3.56 (s, 3H), 5.63 (m, 1H), 6.67 (m, 1H), 6.87-6.98 (m, 4H), 7.15 (m, 2H), 7.27 (m, 1H), 7.29 (m, 1H), 7.32 (m, 1H), 7.55 (m, 1H).

EXAMPLE 34

4108.1002-007 EXAMPLE 461

N-(3-((R)-6-(4-fluorophenyl)-6-(3-hydroxypropyl)-3-((S)-1-(4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-2-oxo-1,3-oxazinan-6-yl)propyl)methanesulfonamide



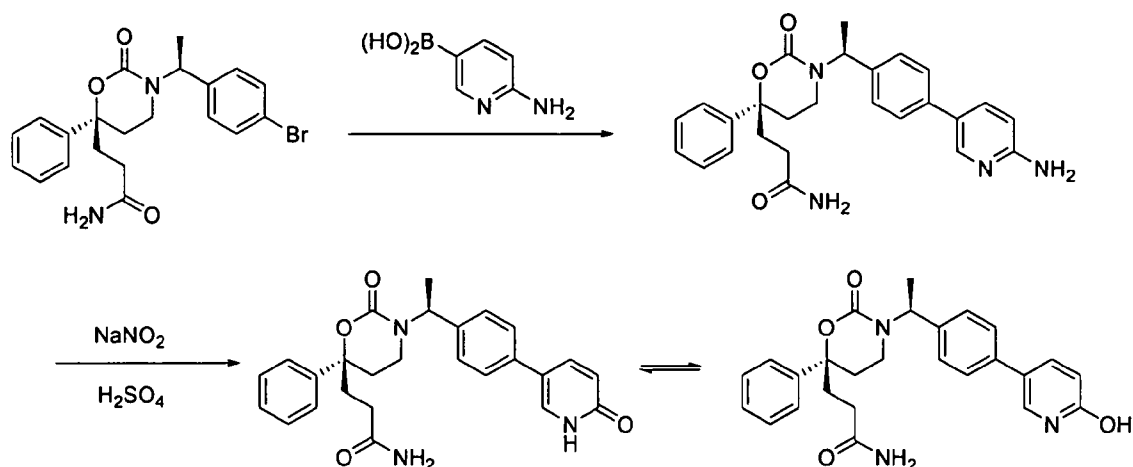
The title compound was prepared from (R)-6-(4-fluorophenyl)-6-(3-hydroxypropyl)-3-((S)-1-(4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-1,3-oxazinan-2-one by treatment with (i) MeSO₂Cl and (ii) MeSO₂NH₂. LC-MS Method 2 t_R = 1.02 min, m/z = 542.3; ¹H NMR (CDCl₃): 1.35 (m, 1H), 1.53 (d, 3H), 1.69 (m, 1H), 1.89 (m, 1H), 2.00 (m, 1H), 2.17-2.33 (m, 3H), 2.89 (s, 3H), 2.97 (m, 1H), 3.06 (m, 2H), 3.66 (s, 3H), 4.38 (s, 1H), 5.67 (m, 1H), 6.82 (d, 1H), 6.99 (m, 4H), 7.15 (m, 2H), 7.22 (m, 2H), 7.47 (s, 1H), 7.63 (d, 1H).

EXAMPLE 35

4108.1002-007 EXAMPLE 484

3-((R)-2-oxo-3-((S)-1-(4-(6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-6-phenyl-1,3-oxazinan-6-yl)propanamide

5



The title compound was prepared from 3-((R)-3-((S)-1-(4-bromophenyl)ethyl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)propanamide following procedures analogous to those described in Example 33 Steps 2 and 3. LC-MS Method 2 t_R = 0.999 min, m/z = 446.1; ^1H NMR (CD_3OD) 1.53 (d, 3H), 1.91-2.01 (m, 1H), 2.18-2.34 (m, 4H), 2.35-2.51 (m, 2H), 3.03-3.12 (m, 1H), 5.56 (m, 1H), 6.62 (d, 2H), 7.03 (d, 2H), 7.24-7.44 (m, 7H), 7.59 (m, 1H), 7.87 (m, 1H).

10

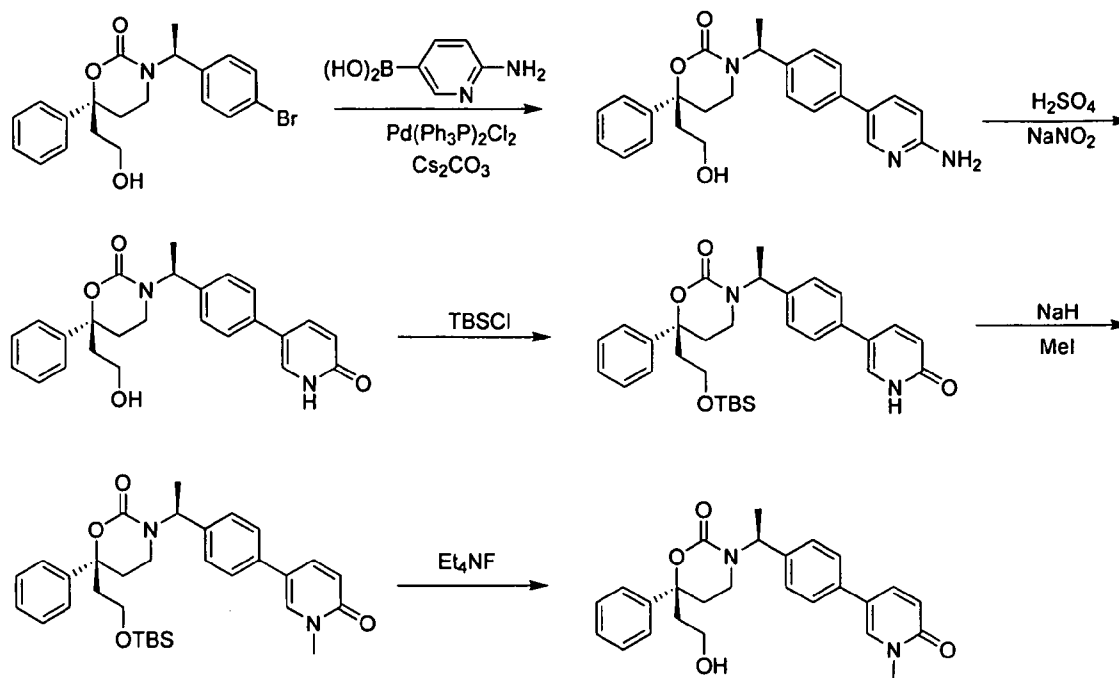
EXAMPLE 36

4108.1002-007 EXAMPLE 485

(S)-6-(2-hydroxyethyl)-3-((S)-1-(4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one

15

- 117 -



The title compound was prepared from (S)-3-((S)-1-(4-bromophenyl)ethyl)-6-(2-hydroxyethyl)-6-phenyl-1,3-oxazinan-2-one using a procedure analogous to that described in Example 33 Steps 2 to 6. LC-MS Method 2 t_R = 1.038 min, m/z = 433.1; ^1H NMR (CDCl_3) 1.48 (d, 3H), 2.06-2.19 (m, 2H), 2.11-2.31 (m, 3H), 2.84 (m, 1H), 3.50 (m, 1H), 3.54 (s, 3H), 3.72 (m, 1H), 5.62 (m, 1H), 6.60 (d, 1H), 6.86 (d, 2H), 7.06 (d, 2H), 7.26 (m, 3H), 7.32 (m, 3H), 7.47 (d, 1H).

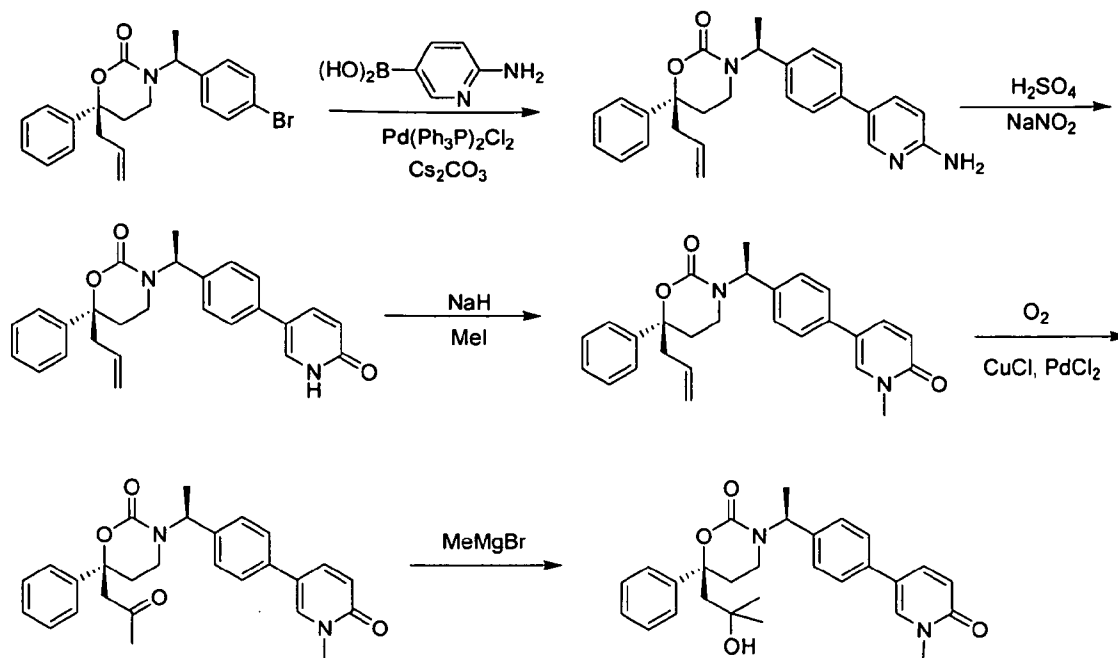
EXAMPLE 37

4108.1002-007 EXAMPLE 486

(S)-6-(2-hydroxy-2-methylpropyl)-3-((S)-1-(4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one

Method 1

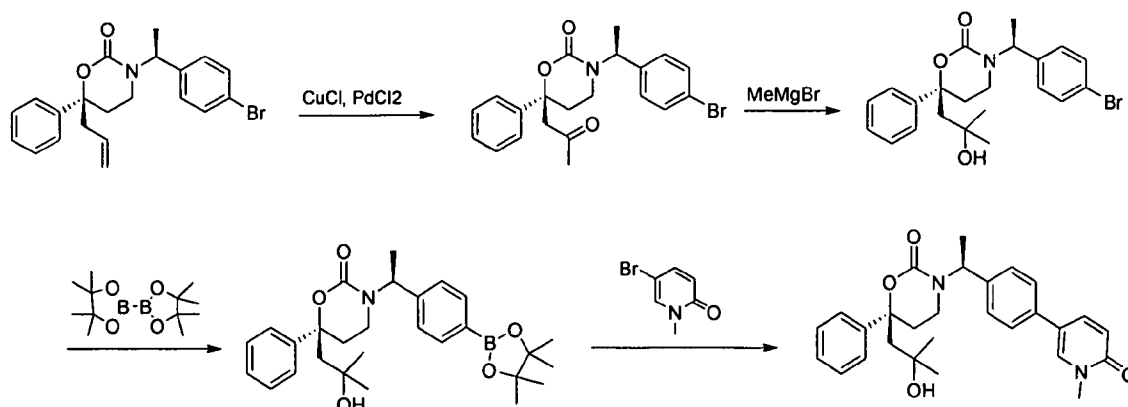
- 118 -



The title compound was prepared from (R)-6-allyl-3-((S)-1-(4-bromophenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one using procedures analogous to those described in Example 33 Steps 2, 3 and 5, followed by procedures analogous to those described in Preparation 1 Method 1

- 5 Steps 4 and 6. LC-MS Method 2 t_R = 1.116 min, m/z = 461.1; ^1H NMR (CDCl_3) 1.09 (s, 3H), 1.16 (s, 3H), 1.51 (m, 3H), 2.05-2.20 (4H), 2.40 (m, 1H), 2.84 (m, 1H), 3.59 (s, 3H), 5.64 (m, 1H), 6.62 (m, 1H), 6.96 (m, 2H), 7.14 (m, 2H), 7.28-7.39 (m, 5H), 7.48 (m, 1H), 7.50 (m, 1H).

Method 2



10

Step 1

To a solution of (R)-6-allyl-3-((S)-1-(4-bromophenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one (20 g, 50 mmol) and CuCl (12.4 g, 125 mmol) in dry DMF (50 mL) was added H_2O (12 mL) and PdCl_2 (2.66 g, 15 mmol) at 0 ~ -5 °C. After addition, the mixture was allowed to warm to rt

gradually for 48 h under O₂. After TLC showing the starting material had disappeared, the solid was filtered off. Water (200 mL) and EtOAc (50 mL) were added. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 40 mL). The combined organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated to give a residue, which was

5 purified by column chromatography to give (S)-3-((S)-1-(4-bromo-phenyl)ethyl)-6-(2-oxopropyl)-6-phenyl-1,3-oxazinan-2-one (12 g, 58%).

Step 2

To a solution of (S)-3-((S)-1-(4-bromophenyl)ethyl)-6-(2-oxopropyl)-6-phenyl-1,3-oxazinan-2-one (12 g, 28.8 mmol) in anhydrous THF (100 mL) was added dropwise

10 methylmagnesium bromide (48 mL, 144 mmol) at -78 °C under nitrogen. The mixture was stirred at rt for 1 h. The reaction mixture was quenched with aqueous NH₄Cl solution (50 mL) in ice water bath. The layers were separated and the aqueous layer was extracted with EtOAc (150 mL). The combined organic phases were washed with brine (30 mL), dried over Na₂SO₄ and

15 concentrated in *vacuo* to give the crude product, which was purified by preparative HPLC and chiral HPLC to afford (S)-3-((S)-1-(4-bromophenyl)ethyl)-6-(2-hydroxy-2-methylpropyl)-6-phenyl-1,3-oxazinan-2-one (6.6 g, 53%).

Step 3

To a solution of (S)-3-((S)-1-(4-bromophenyl)ethyl)-6-(2-hydroxy-2-methylpropyl)-6-phenyl-1,3-oxazinan-2-one (6.6 g, 15.2 mmol) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (6.1 g, 24.3 mmol) in dry DMSO (20 mL) was added KOAc (4.8 g, 48.6 mmol) and Pd(dppf)Cl₂ (372 mg, 0.46 mmol). After addition, the mixture was allowed to warm to 100 °C for 20 h. After TLC showed the starting material had disappeared, the solid was filtered off. Water

25 (60 mL) and EtOAc (20 mL) were added. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated to give a residue, which was purified by column chromatography to give (S)-6-(2-hydroxy-2-methylpropyl)-6-phenyl-3-((S)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl)-1,3-oxazinan-2-one (4.4 g, 60%).

Step 4

To a solution of (S)-6-(2-hydroxy-2-methylpropyl)-6-phenyl-3-((S)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl)-1,3-oxazinan-2-one (2.2 g, 4.58 mmol) and 5-bromo-1-methylpyridin-2(1H)-one (1.37 g, 7.33 mmol) in dry 1,4-dioxane (4 mL) was added

35 aqueous CsCO₃ solution (10 mL, 10 mmol) and Pd(PPh₃)₂Cl₂ (967 mg, 1.38 mmol). After addition, the mixture was heated at 110 °C for 30 min in a microwave. After TLC showed the

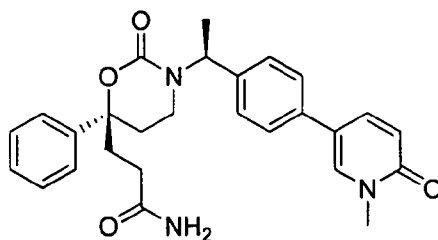
stating material had disappeared, the solid was filtered off. Water (20 mL) and EtOAc (10mL) were added. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated to give a residue, which was purified by preparative HPLC to give (S)-6-(2-hydroxy-2-methylpropyl)-3-((S)-1-(4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one (730 mg, 35%). ¹H NMR (CDCl₃): 1.09 (s, 3H), 1.16 (s, 3H), 1.51 (m, 3H), 2.05-2.20 (4H), 2.40 (m, 1H), 2.84 (m, 1H), 3.59 (s, 3H), 5.64 (m, 1H), 6.62 (m, 1H), 6.96 (m, 2H), 7.14 (m, 2H), 7.28-7.39 (m, 5H), 7.48 (m, 1H), 7.50 (m, 1H).

10

EXAMPLE 38

4108.1002-007 EXAMPLE 487

3-((R)-3-((S)-1-(4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)propanamide



15

The title compound was prepared from (R)-6-allyl-3-((S)-1-(4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one using a procedure analogous to that described in Example 29 Step 2 followed by treatment with (i) Jones reagent and (ii) NH₃, EDC, HOBt. LC-MS Method 2 t_R = 1.028 min, m/z = 460.2; ¹H NMR (CDCl₃) 1.53 (d, 3H), 1.91-2.01 (m, 1H), 2.11-2.42 (m, 5H), 2.46-2.54 (m, 1H), 2.88-2.96 (m, 1H), 3.60 (s, 3H), 5.26 (s, 1H), 5.42 (s, 1H), 5.66 (m, 1H), 6.69 (d, 1H), 6.95-7.03 (d, 2H), 7.12-7.20 (m, 2H), 7.24-7.41 (m, 5H), 7.52 (m, 1H).

20

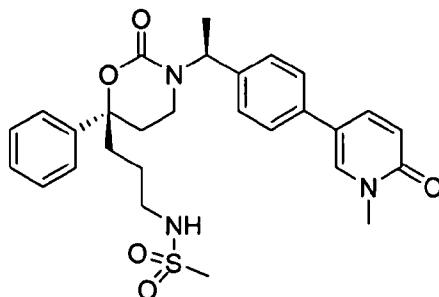
EXAMPLE 39

4108.1002-007 EXAMPLE 488

N-(3-((R)-3-((S)-1-(4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)propyl)methanesulfonamide

25

- 121 -



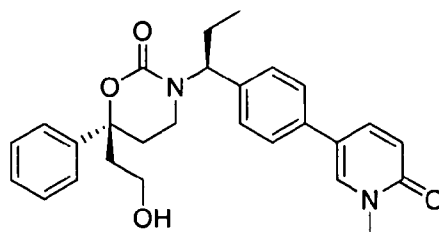
The title compound was prepared from (R)-6-(3-hydroxypropyl)-3-((S)-1-(4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one by treatment with (i) MeSO₂Cl and (ii) MeSO₂NH₂, K₂CO₃. LC-MS Method 2 t_R = 1.095 min, m/z = 524.1; ¹H NMR (CDCl₃) 1.30-1.41 (m, 1H), 1.52 (d, 3H), 1.71 (m, 1H), 1.87-2.07 (m, 3H), 2.09-2.20 (m, 3H), 2.22-2.32 (m, 2H), 2.88 (s, 3H), 3.06 (m, 2H), 3.60 (s, 3H), 4.32 (s, 1H), 5.65 (m, 1H), 6.67 (d, 1H), 6.94 (m, 2H), 7.11 (d, 2H), 7.25 (m, 1H), 7.27-7.40 (m, 4H), 7.53 (dd, 1H).

10

EXAMPLE 40

4108.1002-007 EXAMPLE 499

(S)-6-(2-hydroxyethyl)-3-((S)-1-(4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)propyl)-6-phenyl-1,3-oxazinan-2-one



15

The title compound was prepared from (S)-3-((S)-1-(4-bromophenyl)propyl)-6-(2-hydroxyethyl)-6-phenyl-1,3-oxazinan-2-one following a procedure analogous to that described in Example 18 using 5-bromo-1-methylpyridin-2(1H)-one in Step 2. LC-MS Method 2 t_R = 1.627 min, m/z = 447.1; ¹H NMR (CDCl₃) 1.06 (m, 3H), 1.87-2.06 (m, 2H), 2.11-2.28 (m, 2H), 2.33 (m, 3H), 2.96 (m, 1H), 3.53 (m, 1H), 3.62 (s, 3H), 3.78 (m, 1H), 5.48 (m, 1H), 6.69 (m, 1H), 7.03 (m, 2H), 7.14 (m, 2H), 7.21-7.38 (m, 4H), 7.41 (s, 1H), 7.56 (m, 1H).

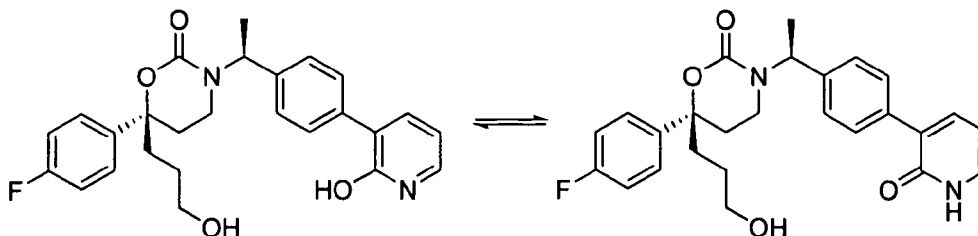
20

EXAMPLE 41

4108.1002-007 EXAMPLE 501

(R)-6-(4-fluorophenyl)-6-(3-hydroxypropyl)-3-((S)-1-(4-(2-oxo-1,2-dihydropyridin-3-yl)phenyl)ethyl)-1,3-oxazinan-2-one

25

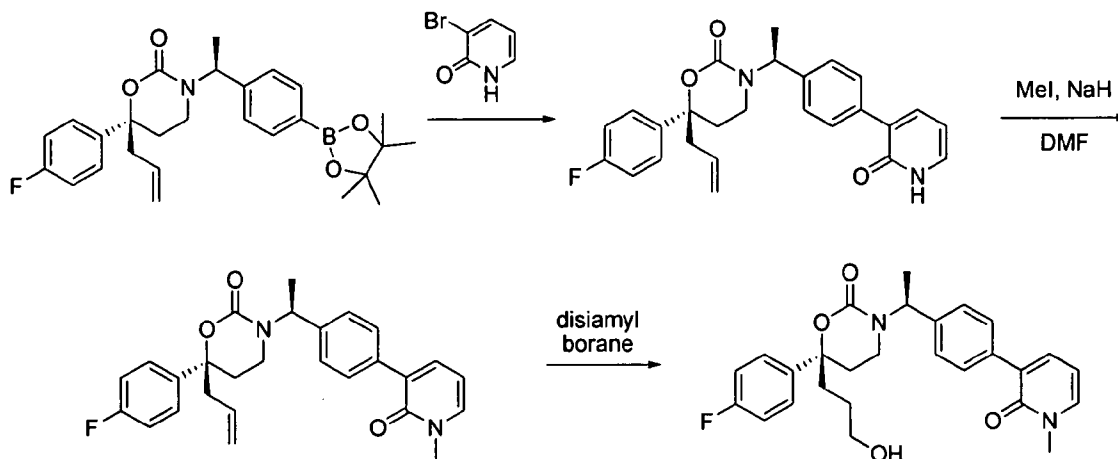


The title compound was prepared from (R)-6-allyl-6-(4-fluorophenyl)-3-((S)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl)-1,3-oxazinan-2-one and 3-bromo-2-hydroxypyridine using a procedure analogous to that described in Example 3 Step 2, followed by a procedure analogous to that described in Example 29 Step 2. LC-MS Method 1 t_R = 1.24, m/z = 452($M+1$); ^1H NMR ($CDCl_3$) 7.76(d, 1H), 7.52(d, 1H), 7.42(dd, 2H), 7.24(m, 2H), 7.08-7.00(m, 4H), 6.75(t, 1H), 5.70(m, 1H), 3.58(t, 1H), 2.94(m, 1H), 1.54(d, 3H).

EXAMPLE 42

4108.1002-007 EXAMPLE 538

(R)-6-(4-fluorophenyl)-6-(3-hydroxypropyl)-3-((S)-1-(4-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)phenyl)ethyl)-1,3-oxazinan-2-one



Step 1

(R)-6-allyl-6-(4-fluorophenyl)-3-((S)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl)-1,3-oxazinan-2-one (18 mg, 0.039 mmol), 3-bromo-2-hydroxypyridine (14 mg, 2 equiv), $Pd(dppf)Cl_2$ (3mg, 10%mol), 2M aq Na_2CO_3 solution (800 μL) and 1,4-dioxane (1.5mL) were mixed. The mixture was evacuated and refilled with N_2 gas (3 x) before being heated overnight at 85 $^\circ C$. After being cooled to rt, the mixture was filtered and acidified with 5% aq HCl solution before being purified by prep HPLC to afford (R)-6-allyl-6-(4-fluorophenyl)-3-((S)-1-(4-(2-

oxo-1,2-dihydropyridin-3-yl)phenyl)ethyl)-1,3-oxazinan-2-one (7.2mg, 43% yield). LC-MS Method 1 t_R =1.57min, m/z 433 ($M+1$).

Step 2

- 5 A solution of (R)-6-allyl-6-(4-fluorophenyl)-3-((S)-1-(4-(2-oxo-1,2-dihydropyridin-3-yl)phenyl)ethyl)-1,3-oxazinan-2-one (15.5 mg, 0.036 mmol) in dry DMF (1 mL) was cooled to 0 °C. Sodium hydride (60% in mineral oil, 3 mg, 2 equiv) was added. After 20 min, iodomethane (4.5 μ L, 2 equiv) was added. The mixture was stirred another 20 min before being warmed to rt slowly and stirred for 2 h. LC-MS found the reaction completed. The mixture was quenched with
10 satd aq NH_4Cl (1mL) and purified by prep HPLC to afford (R)-6-allyl-6-(4-fluorophenyl)-3-((S)-1-(4-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)phenyl)ethyl)-1,3-oxazinan-2-one (13.3 mg, 83% yield). LC-MS Method 1 t_R =1.63min, m/z 447 ($M+1$).

Step 3

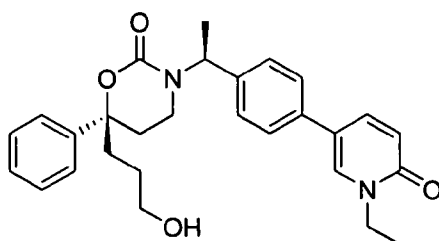
- 15 A solution of (R)-6-allyl-6-(4-fluorophenyl)-3-((S)-1-(4-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)phenyl)ethyl)-1,3-oxazinan-2-one (13.3mg, 0.030mmol) in dry THF (1.5mL) was cooled to 0 °C. Disiamyl borane (0.5M in THF, 500 μ L, excess) was added. After 10 min, the mixture was warmed to rt and stirred for 1 h. The mixture was cooled to 0 °C again, quenched with water (1 mL) and NaBO_3 (10mg). The mixture was concentrated and purified by prep HPLC to afford (R)-
20 6-(4-fluorophenyl)-6-(3-hydroxypropyl)-3-((S)-1-(4-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)phenyl)ethyl)-1,3-oxazinan-2-one (4.2mg, 30% yield). LC-MS Method 1 t_R = 1.33 min, m/z = 487($M+1$); ^1H NMR (CD_3Cl) δ 7.47(dd, 1H), 7.38(m, 3H), 7.24(m, 2H), 7.07(t, 2H), 6.96(d, 2H), 6.39(t, 1H), 5.65(m, 1H), 4.26(t, 1H), 3.66(s, 3H), 2.91(m, 1H), 2.40-2.14(m, 3H), 1.54(d, 3H).

25

EXAMPLE 43

4108.1002-007 EXAMPLE 540

(R)-3-((S)-1-(4-(1-ethyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-6-(3-hydroxypropyl)-6-phenyl-1,3-oxazinan-2-one



30

The title compound was prepared following procedures analogous to those described in Example 30 using ethyl iodide in Step 1, to afford 5-bromo-1-ethylpyridin-2(1H)-one which was used in Step 2. LC-MS Method 2 t_R = 1.297 min, m/z = 461.1; ^1H NMR (CDCl_3) 1.31 (m, 1H),

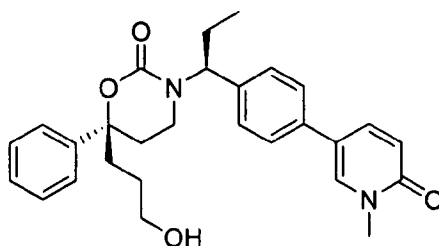
1.36 (t, 3H), 1.51 (d, 3H), 1.68 (m, 1H), 1.86-2.01 (m, 2H), 2.18 (m, 1H), 2.27 (m, 2H), 2.91 (m, 1H), 3.52 (m, 2H), 4.18 (m, 2H), 5.13 (m, 1H), 5.62 (m, 1H), 6.91 (m, 3H), 7.08 (m, 2H), 7.18-7.33 (m, 5H), 7.41 (s, 1H), 7.61 (d, 1H).

5

EXAMPLE 44

4108.1002-007 EXAMPLE 541

(R)-6-(3-hydroxypropyl)-3-((S)-1-(4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)propyl)-6-phenyl-1,3-oxazinan-2-one



10

The title compound was prepared from (R)-6-(3-hydroxypropyl)-6-phenyl-3-((S)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propyl)-1,3-oxazinan-2-one following procedures analogous to those described in Example 30 Step 2. LC-MS Method 2 t_R = 1.113 min, m/z = 461.1; ^1H NMR (CDCl_3) 0.95 (t, 3H), 1.30 (m, 1H), 1.68 (m, 1H), 1.81-1.99 (m, 2H), 2.11-2.32 (m, 3H), 2.88 (m, 1H), 3.50 (m, 2H), 3.58 (m, 2H), 5.43 (m, 1H), 6.49 (d, 1H), 6.98 (d, 2H), 7.08 (d, 2H), 7.19 (m, 1H), 7.25 (m, 4H), 7.32 (s, 1H), 7.47 (m, 1H).

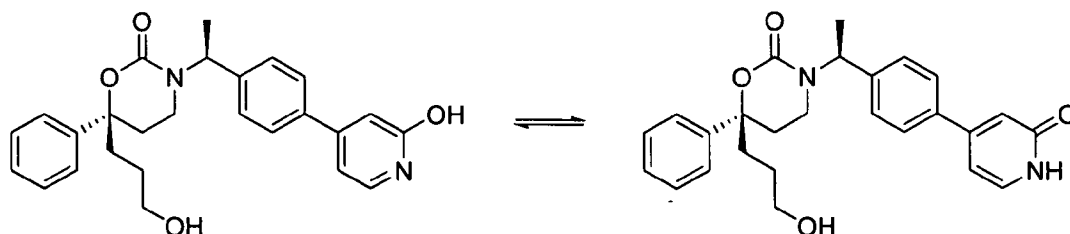
15

EXAMPLE 45

4108.1002-007 EXAMPLE 560

(R)-6-(3-hydroxypropyl)-3-((S)-1-(4-(2-hydroxypyridin-4-yl)phenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one

20



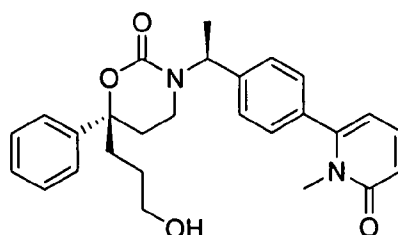
The title compound was prepared from (R)-6-(3-hydroxypropyl)-6-phenyl-3-((S)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl)-1,3-oxazinan-2-one and 4-bromo-2-hydroxypyridine following a procedure analogous to that described in Example 30 Step 2. LC-MS Method 2 t_R = 1.019 min, m/z = 865.4; ^1H NMR (CDCl_3) 1.29-1.40 (m, 1H), 1.49 (d, 3H), 1.60-1.72 (m, 1H), 1.83-2.01 (m, 3H), 2.18 (m, 1H), 2.21-2.37 (m, 2H), 2.88 (m, 1H), 3.51 (m, 2H), 5.63 (m, 1H), 6.41 (d, 1H), 6.68 (s, 1H), 6.90 (d, 2H), 7.21-7.33 (m, 7H), 7.39 (d, 1H).

25

EXAMPLE 46

4108.1002-007 EXAMPLE 565

(R)-6-(3-hydroxypropyl)-3-((S)-1-(4-(1-methyl-6-oxo-1,6-dihydropyridin-2-yl)phenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one



The title compound was prepared from (R)-6-(3-hydroxypropyl)-6-phenyl-3-((S)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl)-1,3-oxazinan-2-one and 6-bromo-1-methylpyridin-2(1H)-one following a procedure analogous to that described in Example 30 Step 2.

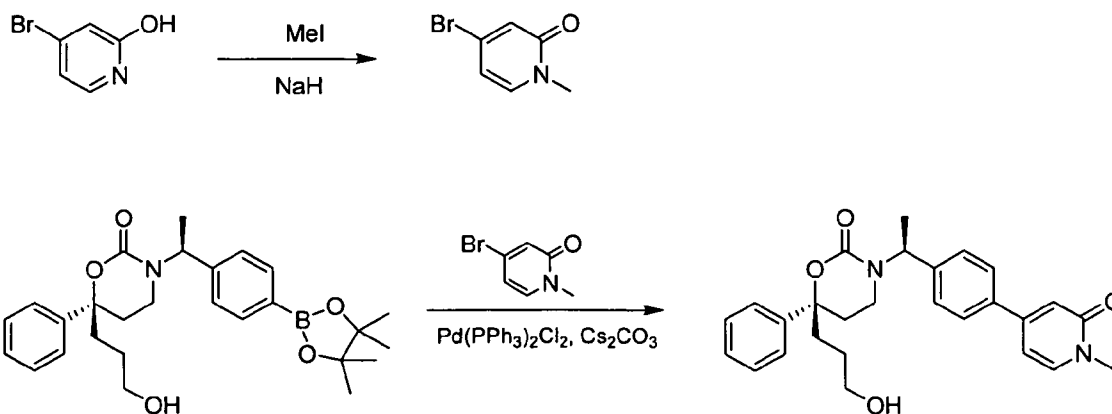
LC-MS Method 2 t_R = 1.088 min, m/z = 447; ^1H NMR ($CDCl_3$) 1.38 (m, 1H), 1.56 (d, 3H), 1.70 (m, 1H), 1.95-2.08 (m, 2H), 2.23 (m, 1H), 2.37 (s, 2H), 3.05 (m, 1H), 3.33 (s, 3H), 3.58 (m, 2H), 5.73 (m, 1H), 6.29 (d, 1H), 6.89 (d, 1H), 7.01-7.09 (m, 4H), 7.21-7.39 (m, 5H), 7.53 (t, 1H).

6-Bromo-1-methylpyridin-2(1H)-one was prepared from 6-bromopyridin-2(1H)-one following a procedure analogous to that described in Example 59 Step 1.

EXAMPLE 47

4108.1002-007 EXAMPLE 566

(R)-6-(3-hydroxypropyl)-3-((S)-1-(4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)phenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one



Step 1

To a suspension of NaH (80 mg, 2 mmol) in THF (10 mL) was added 4-bromopyridin-2-ol (80 mg, 0.46 mmol) at 0 °C. The resulting mixture was stirred for 1 h. Then CH₃I (355 mg, 2.5 mmol) was added to the above mixture, and the mixture was stirred overnight. The reaction was quenched with aqueous NH₄Cl solution. The organic phase was concentrated to give the crude product, which was purified by column to give 4-bromo-1-methylpyridin-2(1*H*)-one (42.3 mg, 50%).

Step 2

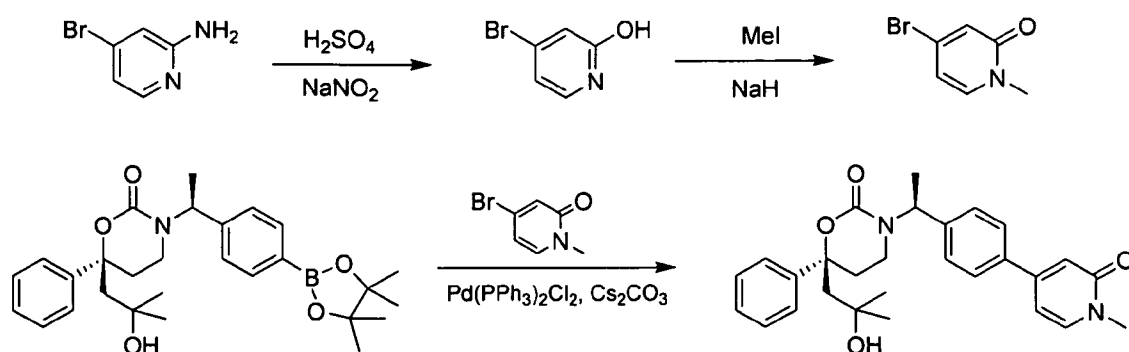
A mixture of (*R*)-6-(3-hydroxypropyl)-6-phenyl-3-((*S*)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl)-1,3-oxazinan-2-one (50 mg, 0.11 mmol) and 4-bromo-1-methylpyridin-2(1*H*)-one (30 mg, 0.16 mmol), Pd(PPh₃)₂Cl₂ (10 mg), and aq. Cs₂CO₃ solution (4 mL, 2 M) in 1,4-dioxane (10 mL) was stirred and heated to reflux for 2 h. When the reaction was over, the mixture was washed with water and extracted with EtOAc. The organic phase was washed with brine, dried over Na₂SO₄, filtered and concentrated to give the crude product, which was purified by preparative TLC to give (*R*)-6-(3-hydroxypropyl)-3-((*S*)-1-(4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)phenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one (25 mg, 51%). ¹H NMR (CDCl₃): δ=1.35 (m, 1H), 1.47 (d, 3H), 1.63 (m, 2H), 1.94 (m, 2H), 2.18 (m, 1H), 2.39 (m, 2H), 2.86 (m, 1H), 3.51 (m, 5H), 5.63 (m, 1H), 6.31 (m, 1H), 6.70 (m, 1H), 6.91 (m, 2H), 7.20-7.32 (m, 8H).

EXAMPLE 48

4108.1002-007 EXAMPLE 588

(*S*)-6-(2-hydroxy-2-methylpropyl)-3-((*S*)-1-(4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)phenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one

Method 1



Step 1

A solution of 4-bromopyridin-2-amine (600 mg, 3.5 mmol) in a mixture of 2 M H₂SO₄ (20 mL) and 2 M Na₂NO₂ (10 mL) was stirred at 0-5°C for 2 h. The reaction mixture was extracted with CH₂Cl₂, and the organic layer was washed with a saturated NaCl solution, dried over anhydrous Na₂SO₄ and concentrated. The residue was purified by preparative TLC to give 4-bromopyridin-2-ol (303 mg, 50%).

Step 2

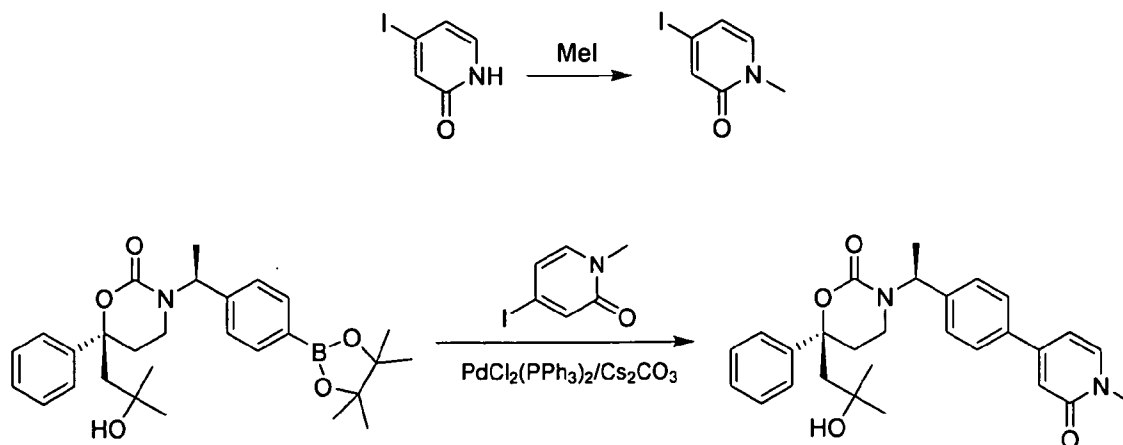
To a suspension of NaH (300 mg, 7.5 mmol) in THF (10 mL) was added 4-bromopyridin-2-ol (303 mg, 1.73 mmol) at 0 °C. After the resulting mixture was stirred for 1 h, CH₃I (491 mg, 3.46 mmol) was added, and the mixture was stirred overnight. The reaction was quenched with aqueous NH₄Cl solution. The organic phase was concentrated to give the crude product, which was purified by column to give 4-bromo-1-methylpyridin-2(1H)-one (161 mg, 50 %).

Step 3

A mixture of (S)-6-(2-hydroxy-2-methylpropyl)-6-phenyl-3-((S)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl)-1,3-oxazinan-2-one (200 mg, 0.42 mmol), 4-bromo-1-methylpyridin-2(1H)-one (118 mg, 0.63 mmol), Pd(Ph₃P)₂Cl₂ (20 mg), and 2 M aq Cs₂CO₃ solution (5 mL, 10 mmol) in 1,4-dioxane (20 mL) was stirred and heated to reflux for 2 h. When the reaction was finished, the mixture was washed with water and extracted with EtOAc. The organic phase was washed with brine, dried over Na₂SO₄, filtered, and concentrated to give the crude product, which was purified by preparative TLC to give (S)-6-(2-hydroxy-2-methylpropyl)-3-((S)-1-(4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)phenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one (83 mg, 43%). LC-MS Method 2 t_R = 1.16 min, m/z = 921.5; ¹H NMR (CDCl₃) 1.11 (s, 3H), 1.18 (s, 3H), 1.22 (t, 1H), 1.52 (m, 3H), 2.21 (s, 2H), 2.22-2.34 (m, 2H), 2.34-2.46 (m, 1H), 2.85 (m, 1H), 3.57 (s, 3H), 5.59 (m, 1H), 6.33 (d, 1H), 6.68 (s, 1H), 7.01 (d, 2H), 7.29-7.41 (m, 8H); ¹H NMR (CD₃OD) 0.98 (s, 3H), 1.29 (s, 3H), 1.58 (d, 3H), 2.17 (s, 2H), 2.22 (m, 1H), 2.50 (m, 2H), 3.08 (m, 1H), 3.59 (s, 3H), 5.59 (m, 1H), 6.61 (d, 1H), 6.66 (s, 1H), 7.08 (m, 2H), 7.30-7.40 (5H), 7.42 (d, 2H), 7.70 (d, 1H).

Method 2

- 128 -



Step 1

To a solution of 4-iodopyridin-2(1H)-one (3 g, 0.013 mol) and K₂CO₃ (3.55 g, 0.026 mol) in DMF (30 mL) was added iodomethane (4.7 g, 0.033 mmol). The mixture was stirred at room temperature overnight. Water and EtOAc were added. The organic phase was dried over Na₂SO₄ and concentrated to give 4-iodo-1-methylpyridin-2(1H)-one (1.6 g, 53%).

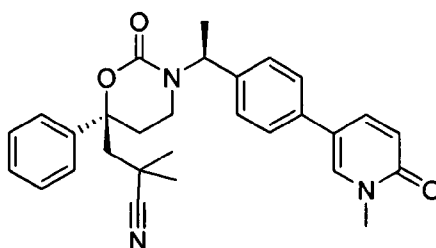
Step 2

A mixture of 4-iodo-1-methylpyridin-2(1H)-one (0.909 g, 3.76 mmol), (S)-6-(2-hydroxy-2-methylpropyl)-6-phenyl-3-((S)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl)-1,3-oxazinan-2-one (1.5 g, 3.13 mmol), 2 M aq Cs₂CO₃ (3 mL, 6 mmol), and PdCl₂(PPh₃)₂ (0.201 g, 0.282 mmol) in 1,4-dioxane (15 mL) was refluxed under N₂ for 2 hours. The reaction mixture was filtered, and the filtrate was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na₂SO₄ and concentrated to obtain the crude compound, which was purified by preparative HPLC and chiral HPLC to obtain (S)-6-(2-hydroxy-2-methylpropyl)-3-((S)-1-(4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)phenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one (399 mg, 28%).

EXAMPLE 49

4108.1002-007 EXAMPLE 593

2,2-dimethyl-3-((R)-3-((S)-1-(4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)propanenitrile



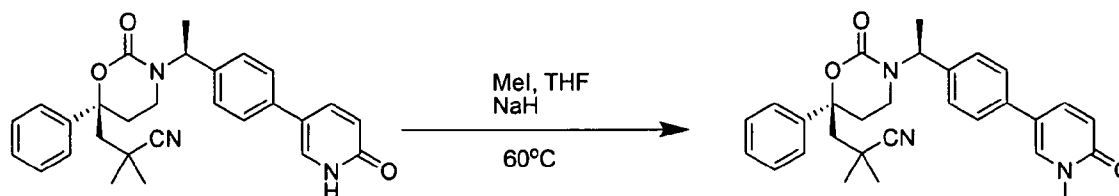
Method 1

The title compound was prepared from 2,2-dimethyl-3-((R)-2-oxo-6-phenyl-3-((S)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl)-1,3-oxazinan-6-yl)propanenitrile and 5-bromo-1-methylpyridin-2(1H)-one following a procedure analogous to that described in Example 6

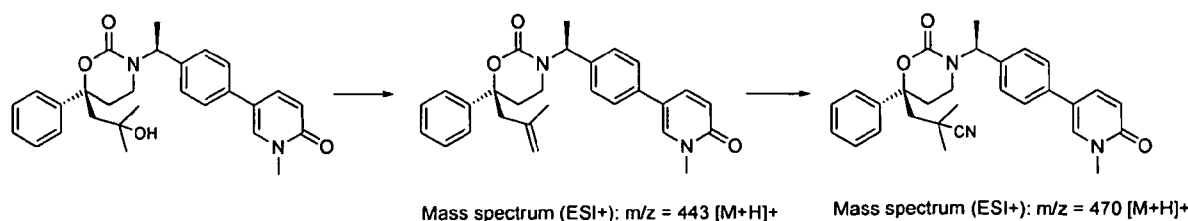
- 5 Step 1. LC-MS Method 2 t_R = 1.231 min, m/z = 470.1; ^1H NMR (CDCl_3) 1.28 (s, 3H), 1.40 (s, 3H), 1.47 (d, 3H), 2.09 (s, 2H), 2.21 (m, 1H), 2.41 (m, 2H), 2.83 (m, 1H), 3.52 (s, 3H), 5.56 (m, 1H), 6.58 (d, 1H), 6.82 (d, 2H), 7.02 (d, 2H), 7.30 (m, 6H), 7.43 (m, 1H).

Method 2

10



- A solution of 2,2-dimethyl-3-((R)-2-oxo-3-((S)-1-(4-(6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-6-phenyl-1,3-oxazinan-6-yl)propanenitrile (202 mg, 0.444 mmol) and MeI (110 μL , 4equiv) in dry THF (5 mL) was cooled to 0 °C. NaH (60% in mineral oil, 36mg, 2equiv) was added. After 10min, the mixture was warmed to rt slowly and stirred for 3 h. LC-MS showed about 50% conversion. The mixture was heated for 1 h at 60 °C. LC-MS found the reaction completed. After cooling to rt, the mixture was cooled to 0 °C and quenched with satd aq NH_4Cl (3 mL). The mixture was then diluted with CH_2Cl_2 (20mL), washed with 1% aq HCl (5 mL) and brine (4 mL), and dried over Na_2SO_4 . After filtration and concentration, the residue was purified by prep HPLC to afford 2,2-dimethyl-3-((R)-3-((S)-1-(4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)propanenitrile (177.4 mg, 85% yield) product as a light brown oil.

Method 3

25

2,2-Dimethyl-3-((R)-3-((S)-1-[4-(1-methyl-6-oxo-1,6-dihydro-pyridin-3-yl)-phenyl]-ethyl)-2-oxo-(S)-6-phenyl-[1,3]oxazinan-6-yl)-propionitrile was prepared from (S)-6-(2-hydroxy-2-methylpropyl)-3-((S)-1-(4-(1-methyl-6-oxo-1,6-dihydropyridin-3-

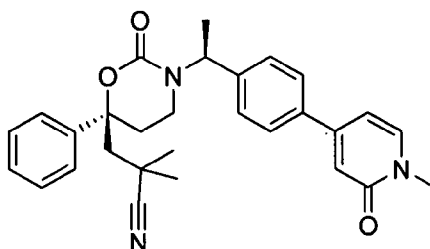
yl)phenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one following procedures analogous to those described Example 71 Method 2 to prepare 3-((R)-3-((S)-1-(4-bromophenyl)ethyl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)-2,2-dimethylpropanenitrile. (S)-6-(2-hydroxy-2-methylpropyl)-3-((S)-1-[4-(1-methyl-6-oxo-1,6-dihydro-pyridin-3-yl)-phenyl]-ethyl)-6-phenyl-[1,3]oxazinan-2-one, is obtained from coupling (S)-6-(2-hydroxy-2-methylpropyl)-6-phenyl-3-[(S)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl]-1,3-oxazinan-2-one with 5-iodo-1-methyl-1H-pyridin-2-one by the action of $\text{Pd}(\text{PPh}_3)_4$ and 2 M aqueous Na_2CO_3 solution in a mixture of methanol and dioxane (1:3) at 80 °C.

10

EXAMPLE 50

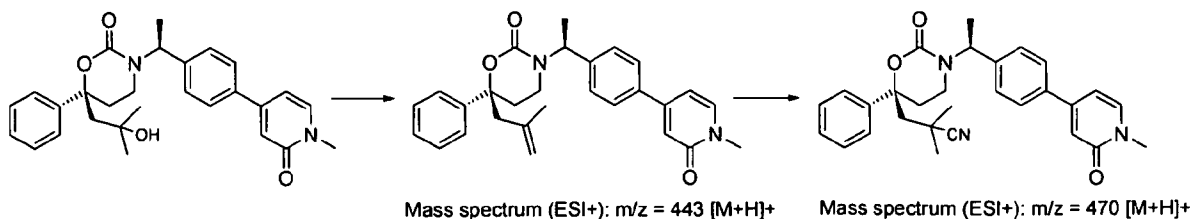
4108.1002-007 EXAMPLE 594[

2,2-dimethyl-3-((R)-3-((S)-1-(4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)phenyl)ethyl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)propanenitrile

15 Method 1

The title compound was prepared from 2,2-dimethyl-3-((R)-2-oxo-6-phenyl-3-((S)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl)-1,3-oxazinan-6-yl)propanenitrile and 4-bromo-1-methylpyridin-2(1H)-one following a procedure analogous to that described in Example 6 Step 1. LC-MS Method 2 t_R = 1.103, m/z = 470.4; ^1H NMR (CDCl_3) 1.26 (s, 3H), 1.41 (s, 3H), 1.49 (d, 3H), 2.09 (s, 2H), 2.24 (m, 1H), 2.53 (m, 2H), 2.88 (m, 1H), 3.56 (s, 3H), 5.59 (m, 1H), 6.38 (d, 1H), 6.78 (s, 1H), 6.84 (d, 2H), 7.19 (m, 2H), 7.31 (m, 6H).

20

Method 2

25

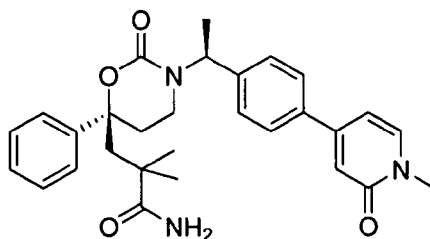
(S)-2,2-Dimethyl-3-(3-{1-[(S)-4-(1-methyl-2-oxo-1,2-dihydro-pyridin-4-yl)-phenyl]-ethyl}-2-oxo-6-phenyl-[1,3]oxazinan-6-yl)-propionitrile was prepared from (S)-6-(2-

hydroxy-2-methylpropyl)-3-((S)-1-(4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)phenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one following procedures analogous to those described in Example 71 Method 2 to prepare 3-((R)-3-((S)-1-(4-bromophenyl)ethyl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)-2,2-dimethylpropanenitrile. The starting compound, (S)-6-(2-hydroxy-2-methyl-propyl)-3-((S)-1-[4-(1-methyl-2-oxo-1,2-dihydro-pyridin-4-yl)-phenyl]-ethyl)-6-phenyl-[1,3]oxazinan-2-one, is obtained from coupling (S)-6-(2-hydroxy-2-methylpropyl)-6-phenyl-3-((S)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl)-1,3-oxazinan-2-one with trifluoro-methanesulfonic acid 1-methyl-2-oxo-1,2-dihydro-pyridin-4-yl ester employing the standard conditions, Pd(dppf)Cl₂·CH₂Cl₂, 2 M aqueous Na₂CO₃ solution, DMF, 90 °C, 2 h.

EXAMPLE 51

4108.1002-007 EXAMPLE 603

2,2-dimethyl-3-((R)-3-((S)-1-(4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)phenyl)ethyl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)propanamide



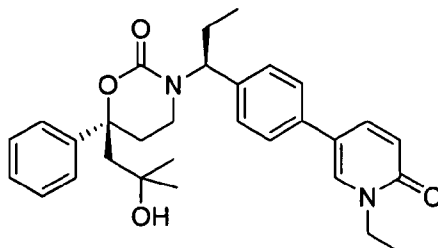
The title compound was prepared from 2,2-dimethyl-3-((R)-2-oxo-6-phenyl-3-((S)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl)-1,3-oxazinan-6-yl)propanenitrile and 4-bromo-1-methylpyridin-2(1H)-one following a procedure analogous to that described in Example 6 Step 1, followed by treatment with H₂O₂, K₂CO₃. LC-MS Method 2 t_R = 1.133 min, m/z = 488.1; ¹H NMR (CDCl₃) 1.12 (s, 3H), 1.19 (s, 3H), 1.49 (d, 3H), 2.09-2.28 (m, 3H), 2.32-2.58 (m, 2H), 2.89 (m, 1H), 3.59 (s, 3H), 5.61 (m, 1H), 6.54 (m, 1H), 6.88 (m, 1H), 6.97-7.10 (m, 2H), 7.28 (m, 6H), 7.42 (m, 1H), 7.53 (m, 1H).

EXAMPLE 52

4108.1002-007 EXAMPLE 614

(S)-3-((S)-1-(4-(1-ethyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)propyl)-6-(2-hydroxy-2-methylpropyl)-6-phenyl-1,3-oxazinan-2-one

- 132 -

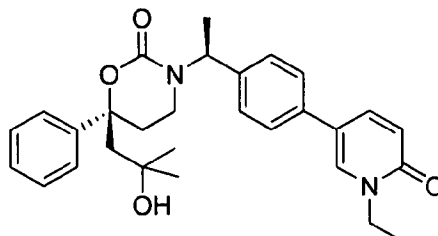


The title compound was prepared from (R)-6-allyl-3-((S)-1-(4-bromophenyl)propyl)-6-phenyl-1,3-oxazinan-2-one following a procedure analogous to that described in Example 32 Method 2 using 5-bromo-1-ethylpyridin-2(1H)-one in Step 4. LC-MS Method 2 t_R = 1.732 min, m/z = 475.1; ^1H NMR (CDCl_3) 0.95 (s, 3H), 1.01 (t, 3H), 1.26 (s, 3H), 1.38 (t, 3H), 2.06 (m, 2H), 2.18-2.31 (m, 3H), 2.36 (m, 1H), 2.55 (m, 1H), 3.04 (m, 1H), 4.11 (m, 2H), 5.37 (m, 1H), 6.66 (d, 1H), 7.11 (m, 2H), 7.20-7.33 (m, 7H), 7.76 (d, 1H), 7.88 (s, 1H).

EXAMPLE 53

4108.1002-007 EXAMPLE 615

(S)-3-((S)-1-(4-(1-ethyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-6-(2-hydroxy-2-methylpropyl)-6-phenyl-1,3-oxazinan-2-one



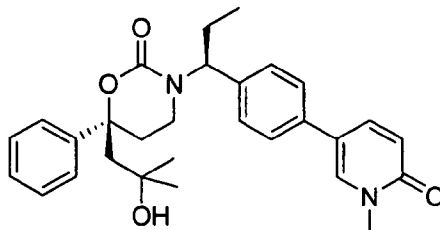
The title compound was prepared from (S)-6-(2-hydroxy-2-methylpropyl)-6-phenyl-3-((S)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl)-1,3-oxazinan-2-one and 5-bromo-1-ethylpyridin-2(1H)-one following a procedure analogous to that described in Example 6 Step 1. LC-MS Method 2 t_R = 1.224 min, m/z = 475.1; ^1H NMR (CDCl_3) 1.11 (s, 3H), 1.19 (s, 3H), 1.39 (t, 3H), 1.56 (d, 3H), 2.20 (s, 2H), 2.26 (m, 1H), 2.36-2.57 (m, 2H), 2.87 (m, 1H), 4.03 (m, 2H), 5.69 (m, 1H), 6.62 (d, 1H), 7.00 (d, 2H), 7.17 (d, 2H), 7.28-7.51 (m, 6H), 7.50 (d, 1H).

EXAMPLE 54

4108.1002-007 EXAMPLE 616

(S)-6-(2-hydroxy-2-methylpropyl)-3-((S)-1-(4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)propyl)-6-phenyl-1,3-oxazinan-2-one

- 133 -

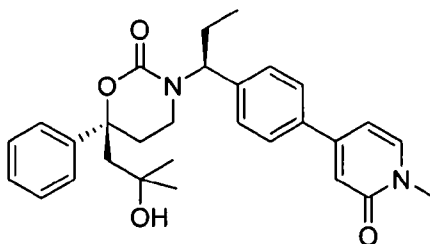


The title compound was prepared from (R)-6-allyl-3-((S)-1-(4-bromophenyl)propyl)-6-phenyl-1,3-oxazinan-2-one following a procedure analogous to that described in Example 32 Method 2 using 5-bromo-1-methylpyridin-2(1H)-one in Step 4. LC-MS Method 2 t_R = 1.746 min, m/z = 475.2; ^1H NMR (CD_3OD) 1.04 (t, 3H), 1.11 (s, 3H), 1.24 (s, 3H), 1.95-2.04 (m, 2H), 2.13-2.26 (m, 4H), 2.44 (m, 1H), 2.91 (m, 1H), 3.61 (s, 3H), 5.36 (m, 1H), 6.67 (d, 1H), 7.10-7.33 (m, 8H), 7.42(s, 1H), 7.55 (d, 1H).

EXAMPLE 55

4108.1002-007 EXAMPLE 618

(S)-6-(2-hydroxy-2-methylpropyl)-3-((S)-1-(4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)phenyl)propyl)-6-phenyl-1,3-oxazinan-2-one



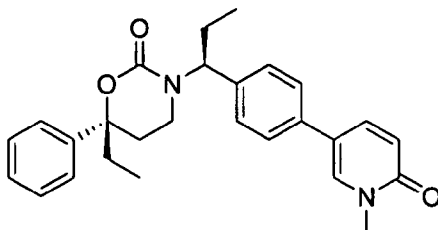
The title compound was prepared from (S)-6-(2-hydroxy-2-methylpropyl)-6-phenyl-3-((S)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propyl)-1,3-oxazinan-2-one and 4-bromo-1-methylpyridin-2(1H)-one following a procedure analogous to that described in Example 59 Step 2. LC-MS Method 2 t_R = 1.203 min, m/z = 971.4; ^1H NMR ($CDCl_3$) 0.97 (t, 3H), 1.12 (s, 3H), 1.19 (s, 3H), 1.79-2.02 (m, 2H), 2.11-2.24 (m, 4H), 2.29-2.42 (m, 1H), 2.81 (m, 1H), 3.50 (s, 3H), 5.40 (m, 1H), 6.28 (d, 1H), 6.64 (s, 1H), 7.02 (d, 2H), 7.18 (m, 3H), 7.20 (m, 2H), 7.28 (m, 3H).

EXAMPLE 56

4108.1002-007 EXAMPLE 622

(R)-6-ethyl-3-((S)-1-(4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)propyl)-6-phenyl-1,3-oxazinan-2-one

- 134 -



The title compound was prepared from (R)-3-((S)-1-(4-bromophenyl)propyl)-6-ethyl-6-phenyl-1,3-oxazinan-2-one following procedures analogous to those described in Example 32 Method 2 Steps 3 and 4. LC-MS Method 1 t_R = 1.6 min, m/z = 431 ($M+1$).

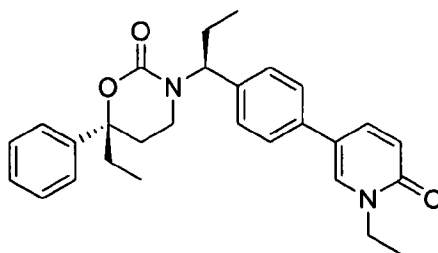
(R)-3-((S)-1-(4-bromophenyl)propyl)-6-ethyl-6-phenyl-1,3-oxazinan-2-one was prepared from 1-chloro-3-phenylpentan-3-ol and (S)-1-(4-bromophenyl)propan-1-amine following a procedure analogous to that described in Example 71 Step 2.

1-chloro-3-phenylpentan-3-ol was prepared from 3-chloro-1-phenylpropan-1-one and ethylmagnesium bromide following a procedure analogous to that described in Preparation 1 Method 1 Step 2.

EXAMPLE 57

4108.1002-007 EXAMPLE 623

(R)-6-ethyl-3-((S)-1-(4-(1-ethyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)propyl)-6-phenyl-1,3-oxazinan-2-one



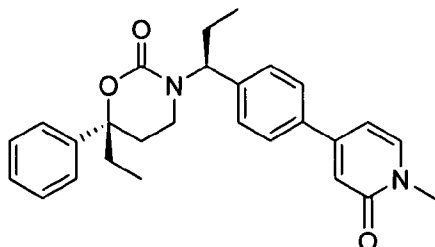
The title compound was prepared from (R)-3-((S)-1-(4-bromophenyl)propyl)-6-ethyl-6-phenyl-1,3-oxazinan-2-one following procedures analogous to those described in Example 32 Method 2 Steps 3 and 4 using 5-bromo-1-ethylpyridin-2(1H)-one in Step 4. LC-MS Method 1 t_R = 1.68 min, m/z = 445 ($M+1$).

EXAMPLE 58

4108.1002-007 EXAMPLE 624

(R)-6-ethyl-3-((S)-1-(4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)phenyl)propyl)-6-phenyl-1,3-oxazinan-2-one

- 135 -



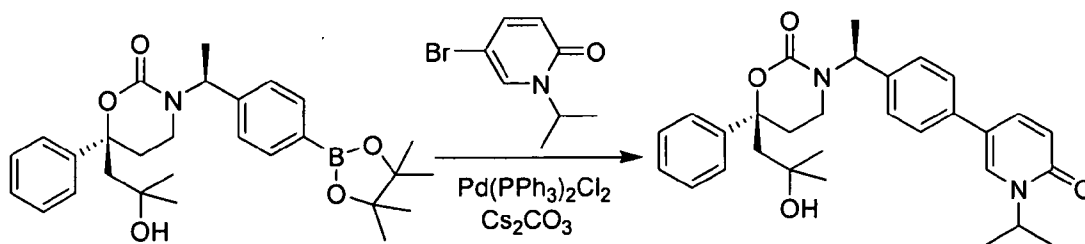
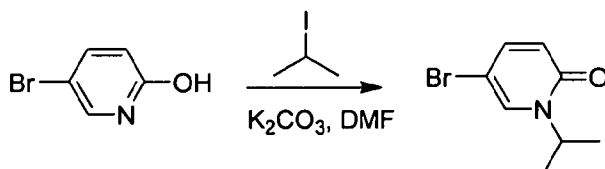
The title compound was prepared from (R)-3-((S)-1-(4-bromophenyl)propyl)-6-ethyl-6-phenyl-1,3-oxazinan-2-one following procedures analogous to those described in Example 32 Method 2 Steps 3 and 4 using 4-iodo-1-methylpyridin-2(1H)-one in Step 4. LC-MS Method 1 t_R = 1.58 min, m/z = 431 (M+1); ^1H NMR (CDCl_3) 7.33 (1H, d, J = 7.03 Hz), 7.29 - 7.21 (7H, m), 7.01 (2H, d, J = 8.20 Hz), 6.75 (1H, d, J = 2.05), 6.39 (1H, dd, J = 2.05, 7.03), 5.48 (1H, ap dd, J = 6.44, 9.66), 3.58 (3H, s), 2.95-2.87 (1H, m), 2.37-2.14 (3H, m), 2.06-1.81 (m, 4H), 1.00 (3H, t, J = 7.32), 0.82 (3H, t, J = 7.61).

10

EXAMPLE 59

4108.1002-007 EXAMPLE 628

(S)-6-(2-hydroxy-2-methylpropyl)-3-((S)-1-(4-(1-isopropyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one



15

Step 1

To a solution of 5-bromopyridin-2-ol (1 g, 5.75 mmol) in DMF (10 mL) were added 2-iodopropane (4.9 g, 28.75 mmol) and K_2CO_3 (4 g, 28.75 mmol). The mixture was stirred at rt overnight. The mixture was diluted with water (20 mL) extracted with EtOAc (3 x 25 mL), the combined organic phase was washed with brine, dried over Na_2SO_4 , concentrated and purified by prep TLC to give 5-bromo-1-isopropylpyridin-2(1H)-one (380 mg, 31 %). ^1H NMR (CDCl_3): 1.35 (d, 6H), 5.65-5.75 (m, 1H), 6.48 (d, 1H), 7.30 (m, 1H), 7.41 (d, 1H).

20

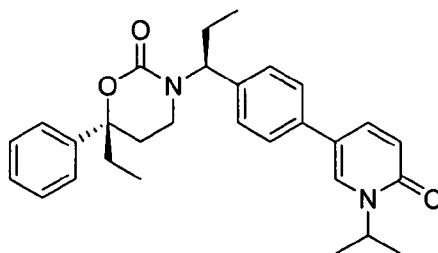
Step 2

To a solution of (S)-6-(2-hydroxy-2-methylpropyl)-6-phenyl-3-((S)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl)-1,3-oxazinan-2-one (100 mg, 0.21 mmol) in 1,4-dioxane (2 mL) was added 5-bromo-1-isopropylpyridin-2(1H)-one (54.2 mg, 0.25 mmol). Then catalysts of Pd(PPh₃)₂Cl₂ (14 mg, 0.02 mmol), Cs₂CO₃ (1 mL, 2 M) were added. The vessel was sealed with a septum and placed into the microwave cavity. Microwave irradiation of 100 W was used, the temperature being ramped from room temperature to 120 °C. Once this temperature was reached, the reaction mixture was held at this temperature for 30 min. After the mixture cooled to rt, the mixture was filtered. The filtrate was extracted with EtOAc (20 mL×4), the organic layer was washed with brine, dried over Na₂SO₄ and concentrated to give the crude product which was purified by preparative HPLC to give (S)-6-(2-hydroxy-2-methylpropyl)-3-((S)-1-(4-(1-isopropyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one (22 mg, 21%). ¹H NMR (CDCl₃): 1.13 (s, 3H), 1.19 (s, 3H), 1.40 (6H), 1.53 (d, 3H), 2.18-2.30 (m, 4H), 2.40 (m, 1H), 2.88 (m, 1H), 5.31 (m, 1H), 5.70 (m, 1H), 6.73 (d, 1H), 7.02 (d, 2H), 7.15 (d, 2H), 7.27-7.38 (m, 5H), 7.43 (d, 1H), 7.50 (d, 1H).

EXAMPLE 60

4108.1002-007 EXAMPLE 630

(R)-6-ethyl-3-((S)-1-(4-(1-isopropyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)propyl)-6-phenyl-1,3-oxazinan-2-one



The title compound was prepared from (R)-3-((S)-1-(4-bromophenyl)propyl)-6-ethyl-6-phenyl-1,3-oxazinan-2-one following procedures analogous to those described in Example 32

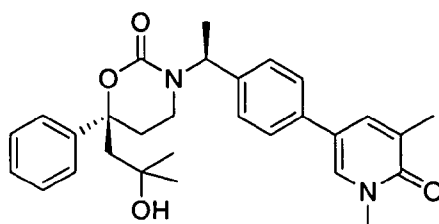
Method 2 Steps 3 and 4 using 5-bromo-1-isopropylpyridin-2(1H)-one in Step 4. LC-MS Method 1 t_R = 1.75 min, m/z = 459 (M+1); ¹H NMR (CDCl₃) 7.49, (1H, dd, J = 2.34, 9.37 Hz), 7.42 (1H, d, J = 2.34 Hz), 7.32-7.24 (5H, m), 7.13 (1H, d, J = 8.20), 7.04 (1H, d, J = 8.49), 6.66 (1H, d, J = 9.37), 5.49 (1H, aq q, J = 6.44, 9.37), 5.33 (1H, m), 2.96-2.91 (1H, m), 2.39-2.32 (1H, m), 2.29-2.17 (2H, m), 2.05-1.85 (m, 4H), 1.41 (6H, dd, J = 1.17, 6.73), 1.01 (3H, t, J = 7.32 Hz), 0.832 (3H, t, J = 7.32 Hz).

5-bromo-1-isopropylpyridin-2(1H)-one was prepared from 5-bromopyridin-2(1H)-one and isopropyl iodide following a procedure analogous to that described in Example 59 Step 1.

EXAMPLE 61

4108.1002-007 EXAMPLE 637

(S)-3-((S)-1-(4-(1,5-dimethyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-6-(2-hydroxy-2-methylpropyl)-6-phenyl-1,3-oxazinan-2-one

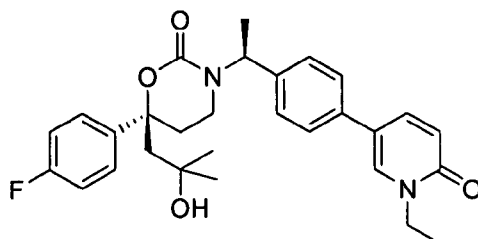


The title compound was prepared following a procedure analogous to that described in Example 59 using 1 5-bromo-3-methylpyridin-2(1H)-one and methyl iodide in Step 1. LC-MS Method 2 t_R = 1.197 min, m/z = 475.1; ^1H NMR ($CDCl_3$) 1.04 (s, 3H), 1.11 (s, 3H), 1.46 (d, 3H), 2.18 (m, 5H), 2.21 (m, 1H), 2.29-2.40 (m, 1H), 2.80 (m, 1H), 3.41 (s, 3H), 3.56 (s, 3H), 5.60 (m, 1H), 6.91 (d, 2H), 7.07 (d, 2H), 7.21-7.40 (m, 7H).

EXAMPLE 62

4108.1002-007 EXAMPLE 638

(S)-3-((S)-1-(4-(1-ethyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-6-(4-fluorophenyl)-6-(2-hydroxy-2-methylpropyl)-1,3-oxazinan-2-one

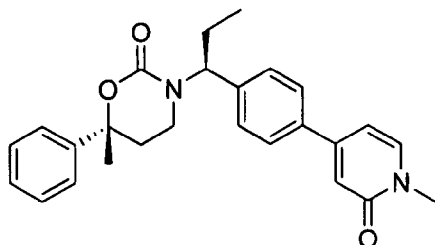


The title compound was prepared following a procedure analogous to that described in Example 59, using 5-bromopyridin-2(1H)-one and ethyl iodide in Step 1 and (S)-6-(4-fluorophenyl)-6-(2-hydroxy-2-methylpropyl)-3-((S)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl)-1,3-oxazinan-2-one in Step 2. LC-MS Method 2 t_R = 1.205 min, m/z = 493.2; ^1H NMR ($CDCl_3$) 1.16 (d, 6H), 1.39 (t, 3H), 1.52 (d, 3H), 2.19 (s, 4H), 2.20-2.31 (m, 2H), 2.38-2.50 (m, 1H), 2.90 (m, 1H), 4.04 (m, 2H), 5.69 (m, 1H), 6.66 (d, 1H), 7.00 (m, 4H), 7.18 (d, 2H), 7.30 (m, 2H), 7.41 (s, 1H), 7.51 (d, 1H).

EXAMPLE 63

4108.1002-007 EXAMPLE 639

(R)-6-methyl-3-((S)-1-(4-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)phenyl)propyl)-6-phenyl-1,3-oxazinan-2-one



The title compound was prepared from (R)-3-((S)-1-(4-bromophenyl)propyl)-6-methyl-6-phenyl-1,3-oxazinan-2-one following procedures analogous to those described in Example 32 Method 2 Steps 3 and 4 using 4-iodo-1-methylpyridin-2(1H)-one in Step 4. LC-MS Method 1 t_R = 1.55 min, m/z = 417 (M+1); ^1H NMR ($CDCl_3$) 7.41 (1H, d, J = 7.03 Hz), 7.33 (2H, d, J = 8.20 Hz), 7.29-7.19 (5H, m), 7.10 (1H, d, J = 8.20), 6.95 (1H, d, J = 1.76), 6.55 (1H, dd, J = 2, 7.03 Hz), 5.51 (1H, q, J = 6.49, 9.66 Hz), 3.65 (3H, s), 3.00-2.95 (1H, m), 2.44-2.36 (1H, m), 2.33-2.15 (2H, m), 2.06-1.86 (2H, m), 1.64 (3H, s), 1.02 (3H, t, J = 7.32 Hz).

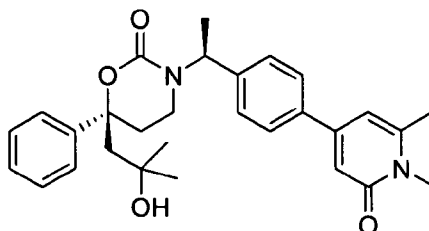
(R)-3-((S)-1-(4-bromophenyl)propyl)-6-methyl-6-phenyl-1,3-oxazinan-2-one was prepared from 4-chloro-2-phenylbutan-2-ol and (S)-1-(4-bromophenyl)propan-1-amine following a procedure analogous to that described in Example 71 Step 2.

4-chloro-2-phenylbutan-2-ol was prepared from 3-chloro-1-phenylpropan-1-one and methylmagnesium bromide following a procedure analogous to that described in Preparation 1 Method 1 Step 2.

EXAMPLE 64

4108.1002-007 EXAMPLE 641

(S)-3-((S)-1-(4-(1,6-dimethyl-2-oxo-1,2-dihydropyridin-4-yl)phenyl)ethyl)-6-(2-hydroxy-2-methylpropyl)-6-phenyl-1,3-oxazinan-2-one



The title compound was prepared from (S)-6-(2-hydroxy-2-methylpropyl)-6-phenyl-3-((S)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propyl)-1,3-oxazinan-2-one and 4-bromo-1,6-dimethylpyridin-2(1H)-one following a procedure analogous to that described in Example 6 Step 1. LC-MS Method 2 t_R = 1.173 min, m/z = 475.2; ^1H NMR ($CDCl_3$) 1.10 (s,

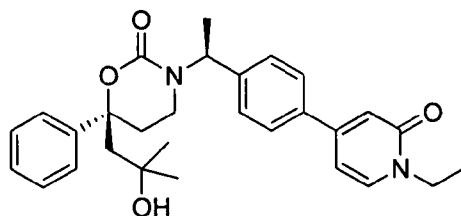
3H), 1.16 (s, 3H), 1.51 (d, 3H), 2.18 (m, 3H), 2.21 (m, 1H), 2.42 (m, 4H), 2.86 (m, 1H), 3.54 (s, 3H), 5.66 (m, 1H), 6.21 (s, 1H), 6.60 (s, 1H), 6.97 (m, 2H), 7.23-7.34 (m, 7H).

4-bromo-1,6-dimethylpyridin-2(1H)-one was prepared by methylation of 4-bromo-6-methylpyridin-2(1H)-one with methyl iodide using K_2CO_3 following a procedure analogous to that described in Example 59 Step 1.

EXAMPLE 65

4108.1002-007 EXAMPLE 642

(S)-3-((S)-1-(4-(1-ethyl-2-oxo-1,2-dihydropyridin-4-yl)phenyl)ethyl)-6-(2-hydroxy-2-methylpropyl)-6-phenyl-1,3-oxazinan-2-one



The title compound was prepared from (S)-6-(2-hydroxy-2-methylpropyl)-6-phenyl-3-((S)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propyl)-1,3-oxazinan-2-one and 1-ethyl-4-iodopyridin-2(1H)-one following a procedure analogous to that described in Example 6 Step 1.

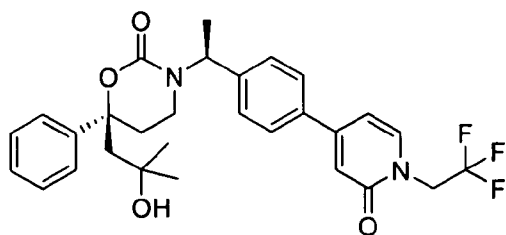
LC-MS Method 2 t_R = 1.228 min, m/z = 971.4; ^1H NMR ($CDCl_3$) 1.10 (s, 3H), 1.14 (s, 3H), 1.36 (m, 3H), 1.53 (d, 3H), 2.17 (s, 2H), 2.21-2.32 (m, 2H), 2.32-2.48 (m, 1H), 2.88 (m, 1H), 4.00 (m, 2H), 5.68 (m, 1H), 6.39 (d, 1H), 6.78 (s, 1H), 6.99 (d, 2H), 7.27-7.38 (m, 8H).

1-ethyl-4-iodopyridin-2(1H)-one was prepared from 4-iodopyridin-2(1H)-one and ethyl iodide following a procedure analogous to that described in Example 59 Step 1.

EXAMPLE 66

4108.1002-007 EXAMPLE 643

(S)-6-(2-hydroxy-2-methylpropyl)-3-((S)-1-(4-(2-oxo-1-(2,2,2-trifluoroethyl)-1,2-dihydropyridin-4-yl)phenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one



The title compound was prepared from (S)-6-(2-hydroxy-2-methylpropyl)-6-phenyl-3-((S)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propyl)-1,3-oxazinan-2-one and 4-iodo-1-(2,2,2-trifluoroethyl)pyridin-2(1H)-one following a procedure analogous to that described in

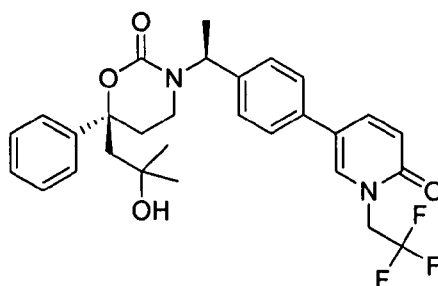
Example 6 Step 1. LC-MS Method 2 t_R = 1.871 min, m/z = 471.1; ^1H NMR ($CDCl_3$) 1.11 (s, 3H), 1.17 (s, 3H), 1.53 (d, 3H), 2.16-2.33 (m, 4H), 2.35-2.47 (m, 1H), 2.89 (m, 1H), 4.58-4.70 (m, 2H), 5.69 (m, 1H), 6.71 (s, 1H), 7.00 (d, 2H), 7.19-7.38 (m, 8H).

4-iodo-1-(2,2,2-trifluoroethyl)pyridin-2(1H)-one was prepared from 4-iodopyridin-2(1H)-one and 2,2,2-trifluoroethyl trifluoromethanesulfonate following a procedure analogous to that described in Example 59 Step 1.

EXAMPLE 67

4108.1002-007 EXAMPLE 646

(S)-6-(2-hydroxy-2-methylpropyl)-3-((S)-1-(4-(6-oxo-1-(2,2,2-trifluoroethyl)-1,6-dihydropyridin-3-yl)phenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one



The title compound was prepared from (S)-6-(2-hydroxy-2-methylpropyl)-6-phenyl-3-((S)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propyl)-1,3-oxazinan-2-one and 5-bromo-1-(2,2,2-trifluoroethyl)pyridin-2(1H)-one following a procedure analogous to that described in Example 6 Step 1. LC-MS Method 2 t_R = 1.323 min, m/z = 471.1; ^1H NMR ($CDCl_3$) 1.13 (s, 3H), 1.19 (s, 3H), 1.53 (d, 3H), 2.19-2.30 (m, 4H), 2.40 (m, 1H), 2.89 (m, 1H), 4.67 (m, 2H), 5.69 (m, 1H), 6.70 (d, 1H), 7.03 (d, 2H), 7.13 (d, 2H), 7.29-7.38 (m, 6H), 7.55 (d, 1H).

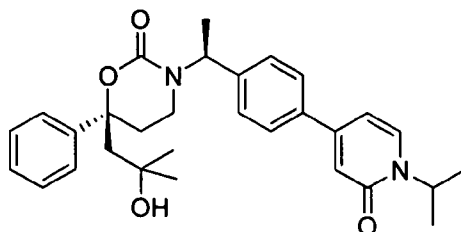
5-bromo-1-(2,2,2-trifluoroethyl)pyridin-2(1H)-one was prepared from 5-bromopyridin-2(1H)-one and 2,2,2-trifluoroethyl trifluoromethanesulfonate following a procedure analogous to that described in Example 59 Step 1.

EXAMPLE 68

4108.1002-007 EXAMPLE 647

(S)-6-(2-hydroxy-2-methylpropyl)-3-((S)-1-(4-(1-isopropyl-2-oxo-1,2-dihydropyridin-4-yl)phenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one

- 141 -



The title compound was prepared from (S)-6-(2-hydroxy-2-methylpropyl)-6-phenyl-3-((S)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propyl)-1,3-oxazinan-2-one and 4-iodo-1-isopropylpyridin-2(1H)-one following a procedure analogous to that described in Example 6 Step

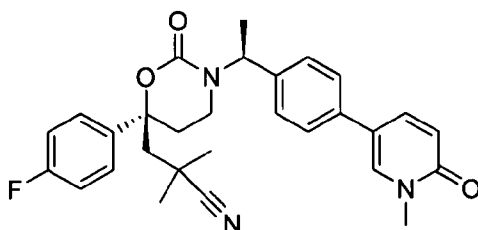
1. LC-MS Method 2 t_R = 1.846 min, m/z = 489.2; ^1H NMR ($CDCl_3$) 1.10 (s, 3H), 1.24 (s, 3H), 1.39 (d, 6H), 1.52 (d, 3H), 2.17-2.31 (m, 4H), 2.35-2.46 (m, 1H), 2.88 (m, 1H), 5.27 (m, 1H), 5.69 (m, 1H), 6.49 (d, 1H), 6.88 (s, 1H), 7.00 (d, 2H), 7.29-7.38 (m, 7H), 7.40 (d, 1H).

4-iodo-1-isopropylpyridin-2(1H)-one was prepared from 4-iodopyridin-2(1H)-one and isopropyl iodide following a procedure analogous to that described in Example 59 Step 1.

EXAMPLE 69

4108.1002-007 EXAMPLE 651

3-((R)-6-(4-fluorophenyl)-3-((S)-1-(4-(1-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-2-oxo-1,3-oxazinan-6-yl)-2,2-dimethylpropanenitrile



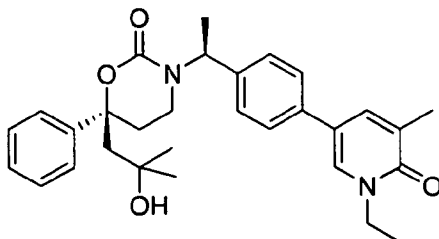
The title compound was prepared from 3-((R)-6-(4-fluorophenyl)-2-oxo-3-((S)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl)-1,3-oxazinan-6-yl)-2,2-dimethylpropanenitrile and 5-bromo-1-methylpyridin-2(1H)-one following a procedure analogous to that described in Example 3 Step 2. LC-MS Method 1 t_R = 1.45 min, m/z = 488; ^1H NMR ($CDCl_3$) 7.68(dd, 1H), 7.52(d, 1H), 7.32(q, 2H), 7.17(d, 2H), 7.06(t, 2H), 6.97(d, 2H), 6.91(d, 1H), 5.66(q, 1H), 3.72(s, 3H), 2.99(dt, 1H), 2.48(dd, 2H), 2.27(m, 1H), 2.11(s, 2H), 1.55(d, 3H), 1.44(s, 3H), 1.34(s, 3H).

EXAMPLE 70

4108.1002-007 EXAMPLE 655

(S)-3-((S)-1-(4-(1-ethyl-5-methyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-6-(2-hydroxy-2-methylpropyl)-6-phenyl-1,3-oxazinan-2-one

- 142 -



The title compound was prepared from (S)-6-(2-hydroxy-2-methylpropyl)-6-phenyl-3-((S)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl)-1,3-oxazinan-2-one and 5-bromo-1-ethyl-3-methylpyridin-2(1H)-one following a procedure analogous to that described in Example 6 Step 1. LC-MS Method 2 t_R = 1.314 min, m/z = 489; ^1H NMR ($CDCl_3$) 1.09 (s, 3H), 1.15 (s, 3H), 1.35 (t, 3H), 1.50 (d, 3H), 2.15-2.25 (m, 7H), 2.35 (m, 1H), 2.86 (m, 1H), 4.03 (m, 2H), 5.66 (q, 1H), 6.96 (d, 2H), 7.13 (d, 2H), 7.25-7.36 (m, 7H).

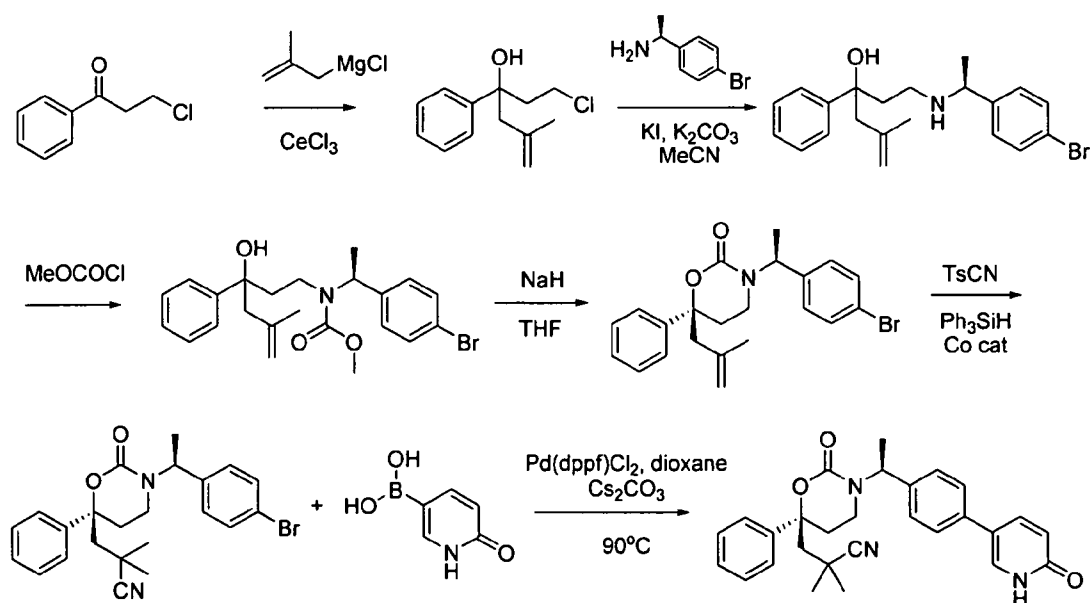
5-Bromo-1-ethyl-3-methylpyridin-2(1H)-one was prepared by alkylation of 5-bromo-3-methylpyridin-2(1H)-one with ethyl iodide following a procedure analogous to that described in Example 59 Step 1.

EXAMPLE 71

4108.1002-007 EXAMPLE 658

2,2-dimethyl-3-((R)-2-oxo-3-((S)-1-(4-(6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-6-phenyl-1,3-oxazinan-6-yl)propanenitrile

Method 1



Step 1

A 250 mL flask was charged with anhydrous CeCl_3 (7.1890 g, 29.2 mmol) and THF (55 mL). The mixture was vigorously stirred for 2 h at rt. The suspension was then cooled to -78°C and a solution of 2-methylallylmagnesium chloride (0.5 M in THF, 56 mL, 28.0 mmol) was added.

- 5 After stirring for 2 h at -78°C , a solution of 3-chloropropiophenone (3.350 g, 19.8 mmol) in THF (30 mL) was added via cannula. The reaction mixture was allowed to slowly warm to 8°C while stirring overnight (18 h). The reaction was then quenched with satd aq NaHCO_3 , extracted with EtOAc, and dried over Na_2SO_4 . After the solvents were evaporated, the crude 1-chloro-5-methyl-3-phenylhex-5-en-3-ol was directly used in the next step without further purification. LC-MS
- 10 Method 1 $t_R = 1.91$ min, m/z 248, 207 ($\text{M}-\text{OH}^+$); ^1H NMR (400 MHz, CDCl_3) δ 7.39-7.22 (m, 5H), 4.92 (m, 1H), 4.77 (m, 1H), 3.60-3.53 (m, 1H), 3.17-3.10 (m, 1H), 2.67 (d, $J = 13.2$ Hz, 1H), 2.55 (d, $J = 13.2$ Hz, 1H), 2.41-2.25 (m, 2H), 1.29 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 144.55, 141.72, 128.32, 126.88, 125.07, 116.50, 74.44, 51.46, 46.34, 40.19, 24.22.

15 Step 2

1-chloro-5-methyl-3-phenylhex-5-en-3-ol (1.28 g, 5.7 mmol), (S)-1-(4-bromophenyl)ethanamine (1.37 g, 1.2 equiv), KI (995 mg, 1.05 equiv), K_2CO_3 (1.57 g, 2 equiv) were mixed with acetonitrile (15 mL) and heated to reflux (oil bath 96°C) for overnight. After being cooled to rt, the mixture was filtered, concentrated, and purified by chromatography on a

20 40-g silica gel column, eluted with 0~8% MeOH in CH_2Cl_2 , to afford 1-((S)-1-(4-bromophenyl)ethylamino)-5-methyl-3-phenylhex-5-en-3-ol (1.33 g, 60%).

Step 3

- To a solution of 1-((S)-1-(4-bromophenyl)ethylamino)-5-methyl-3-phenylhex-5-en-3-ol
- 25 (1.33 g, 3.43 mmol) in CH_2Cl_2 (100 mL) was added pyridine (277 μL , 1 equiv) and triethylamine (717 μL , 1.5equiv). The mixture was cooled to 0°C . Methyl chloroformate (397 μL , 1.5 equiv) was added slowly. After 15 min, the mixture was warmed to rt slowly and stirred for 3 h. The mixture was then diluted with ether (200 mL), washed with 5% aq HCl (2 x 25 mL), satd aq NaHCO_3 (25 mL) and brine (20 mL), and dried over Na_2SO_4 . After filtration and concentration, the
- 30 crude methyl (S)-1-(4-bromophenyl)ethyl(3-hydroxy-5-methyl-3-phenylhex-5-enyl)carbamate was used for next steps without further purification.

Step 4

- The crude methyl (S)-1-(4-bromophenyl)ethyl(3-hydroxy-5-methyl-3-phenylhex-5-enyl)carbamate from above procedure was dissolved in dry THF (75 mL), NaH (60% in mineral oil, 274 mg, 2 equiv) was added slowly at rt. After 10 min, the mixture was heated to reflux for 2 h. LC-MS found reaction completed. The mixture was cooled to 0°C , quenched with satd aq NH_4Cl
- 35

(10 mL), diluted with ether (100 mL), washed with 1% aq HCl (25 mL) and brine (15 mL), and dried over Na₂SO₄. After filtration and concentration, the crude product was purified by chromatography on a 40-g silica gel column, eluted with 10~35% EtOAc in hexanes. The second UV active peak was collected to afford (R)-3-((S)-1-(4-bromophenyl)ethyl)-6-(2-methylallyl)-6-phenyl-1,3-oxazinan-2-one (490mg 34.5% overall yield for Steps 3 and 4).

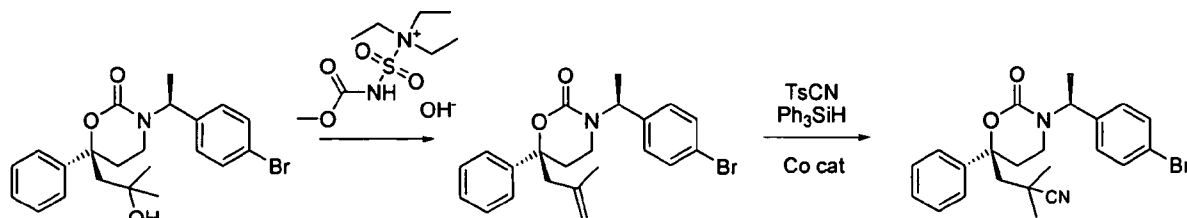
Step 5

A mixture of (R)-3-((S)-1-(4-bromophenyl)ethyl)-6-(2-methylallyl)-6-phenyl-1,3-oxazinan-2-one (490 mg, 1.18 mmol), TsCN (257 mg, 1.2 equiv), PhSiH₃ (157 μ L, 1.07 equiv) and the cobalt *N,N'*-bis(3,5-di-*tert*-butylsalicylidene)-1,1,2,2-tetramethylethylenediamine catalyst prepared as described in Preparation 3 (7.5 mg, 0.01 equiv) and ethanol (20 mL) was stirred 4 h at rt. LC-MS found the reaction completed. The mixture was concentrated and purified by ISCO (40g column, 25~80% EtOAc in Hexanes) to afford 267mg product (51% yield). LC-MS Method 1 t_R = 1.89min., m/z 441, 443 (M+1).

Step 6

To a solution of 3-((R)-3-((S)-1-(4-bromophenyl)ethyl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)-2,2-dimethylpropanenitrile (208mg, 0.47mmol) in 1,4-dioxane (5 mL) were added 6-oxo-1,6-dihydropyridin-3-ylboronic acid (98mg, 1.5 equiv), 2.0 M aq Cs₂CO₃ solution (500 μ L), and Pd(dppf)Cl₂ (20mg, 0.06 equiv). The mixture was degassed and refilled with N₂ gas 3 times, before being heated to 90 °C (oil bath) for 3 h. LC-MS found the reaction was complete. The mixture was cooled to rt, diluted with EtOAc (25 mL), and washed with water (10 mL). The aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with water (10 mL) and brine (8 mL), and dried over Na₂SO₄. After filtration and concentration, the residue was purified by chromatography (12-g silica gel cartridge, 0 ~10% MeOH in CH₂Cl₂, major UV peak) to afford 2,2-dimethyl-3-((R)-2-oxo-3-((S)-1-(4-(6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-6-phenyl-1,3-oxazinan-6-yl)propanenitrile (202 mg, 94%) as a brown oil. LC-MS Method 1 t_R = 1.34 min, m/z = 456 (M+1); ¹H NMR (CDCl₃) 8.01 (d, 1H), 7.80 (s, 1H), 7.36 (dt, 6H), 7.19 (d, 2H), 6.98 (m, 3H), 5.65 (d, 1H), 2.98 (d, 1H), 2.50 (m, 2H), 2.32 (m, 1H), 2.17 (s, 2H), 1.57 (d, 3H), 1.40 (s, 3H), 1.32 (s, 3H).

Method 2



Step 1. 3-[(S)-1-(4-Bromo-phenyl)-ethyl]-(S)-6-(2-methyl-allyl)-6-phenyl-[1,3]oxazinan-2-one

(Methoxycarbonylsulfamoyl)triethylammonium hydroxide (1.38 g) was added to 3-[(S)-1-(4-bromo-phenyl)-ethyl]-(S)-6-(2-hydroxy-2-methyl-propyl)-6-phenyl-[1,3]oxazinan-2-one (2.0 g) dissolved in tetrahydrofuran (30 mL) and toluene (15 mL). The resulting solution was stirred at room temperature for 0.5 h and at 75 °C for 1 h. After cooling to room temperature, the solution was concentrated and ethyl acetate was added to the residue. The resulting mixture was washed with aqueous NaHCO₃ solution and brine and dried (MgSO₄). The title compound was obtained after removal of the solvent. Yield: 1.9 g (quantitative). Mass spectrum (ESI⁺): m/z = 414/416 (Br) [M+H]⁺

Step 2. 3-[(S)-1-(4-Bromo-phenyl)-ethyl]-2-oxo-(S)-6-phenyl-[1,3]oxazinan-6-yl]-2,2-dimethyl-propionitrile

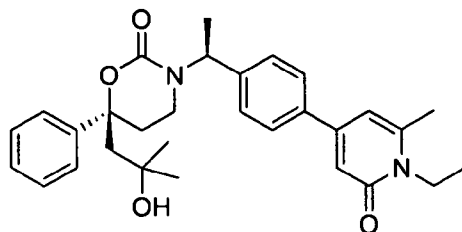
3-[(S)-1-(4-Bromo-phenyl)-ethyl]-(S)-6-(2-methyl-allyl)-6-phenyl-[1,3]oxazinan-2-one (0.21 g), p-toluenesulfonyl cyanide (143 mg), tert-BuOOH (5.5 M in decane, 27 µL), and phenylsilane (64 µL) were added in the given order to a flask charged with a stir bar, (1*R*,2*R*)-(-)-1,2-cyclohexanediamino-*N,N'*-bis(3,5-di-*tert*-butylsalicyliden)cobalt(II) (3 mg) and ethanol (15 mL) in argon atmosphere. The resulting solution was stirred at room temperature for 3 h and then concentrated under reduced pressure. The residue was purified by chromatography on silica gel (cyclohexane/ethyl acetate 60:40→0:100) to afford the title compound as a resin-like solid. Yield: 0.16 g (70% of theory). Mass spectrum (ESI⁺): m/z = 441/443 (Br) [M+H]⁺

EXAMPLE 72

4108.1002-007 EXAMPLE 659

(S)-3-((S)-1-(4-(1-ethyl-6-methyl-2-oxo-1,2-dihydropyridin-4-yl)phenyl)ethyl)-6-(2-hydroxy-2-methylpropyl)-6-phenyl-1,3-oxazinan-2-one

- 146 -



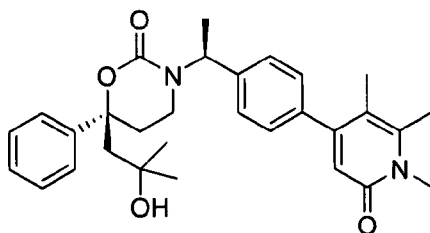
The title compound was prepared from (S)-6-(2-hydroxy-2-methylpropyl)-6-phenyl-3-((S)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl)-1,3-oxazinan-2-one and 4-bromo-1-ethyl-6-methylpyridin-2(1H)-one following a procedure analogous to that described in Example 6 Step 1. LC-MS Method 2 t_R = 1.211 min, m/z = 489.2; ^1H NMR ($CDCl_3$) 1.10 (s, 3H), 1.17 (s, 3H), 1.49 (s, 9H), 1.57 (d, 3H), 2.22 (m, 4H), 2.37 (m, 1H), 2.84 (m, 1H), 5.60 (m, 1H), 5.91 (s, 1H), 7.06 (d, 2H), 7.27-7.40 (m, 5H), 7.68 (d, 1H), 7.24 (d, 2H), 8.09 (d, 1H), 8.90 (s, 1H).

4-bromo-1-ethyl-6-methylpyridin-2(1H)-one was prepared by alkylation of 4-bromo-6-methylpyridin-2(1H)-one with ethyl iodide using K_2CO_3 following a procedure analogous to that described in Example 59 Step 1.

EXAMPLE 73

4108.1002-007 EXAMPLE 664

(S)-6-(2-hydroxy-2-methylpropyl)-6-phenyl-3-((S)-1-(4-(1,5,6-trimethyl-2-oxo-1,2-dihydropyridin-4-yl)phenyl)ethyl)-1,3-oxazinan-2-one



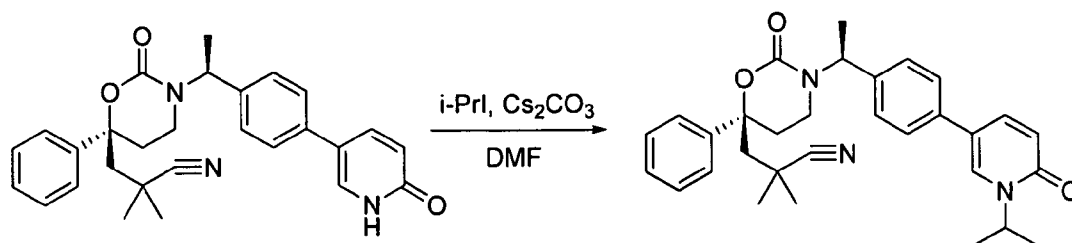
The title compound was prepared from (S)-6-(2-hydroxy-2-methylpropyl)-6-phenyl-3-((S)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl)-1,3-oxazinan-2-one and 4-bromo-1,5,6-trimethylpyridin-2(1H)-one following a procedure analogous to that described in Example 6 Step 1. LC-MS Method 2 t_R = 1.187 min, m/z = 489.2; ^1H NMR ($CDCl_3$) 1.10 (s, 3H), 1.15 (s, 3H), 1.32 (m, 3H), 1.52 (m, 3H), 1.72 (s, 1H), 2.18 (m, 3H), 2.19 (m, 1H), 2.42 (m, 4H), 2.86 (m, 1H), 4.12 (m, 2H), 5.66 (m, 1H), 6.16 (s, 1H), 6.53 (s, 1H), 6.98 (m, 2H), 7.23-7.34 (m, 7H).

4-bromo-1,5,6-trimethylpyridin-2(1H)-one was prepared by alkylation of 4-bromo-5,6-dimethylpyridin-2(1H)-one with methyl iodide using K_2CO_3 following a procedure analogous to that described in Example 59 Step 1. 4-bromo-5,6-dimethylpyridin-2(1H)-one was prepared following the procedure described in McElroy, W. T. and DeShong, P. *Org. Lett.* **2003**, 5, 4779.

EXAMPLE 74

4108.1002-007 EXAMPLE 690

3-((R)-3-((S)-1-(4-(1-isopropyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)-2,2-dimethylpropanenitrile

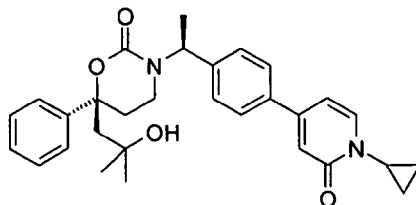


2,2-dimethyl-3-((R)-2-oxo-3-((S)-1-(4-(6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-6-phenyl-1,3-oxazinan-6-yl)propanenitrile (6 mg, 0.013 mmol) was dissolved in DMF (2.5 mL). Cs_2CO_3 (c.a. 15 mg, excess) and *i*-PrI (100 μL , excess) were added. The mixture was stirred for 3 h at rt. LC-MS found the reaction was complete. The mixture was purified by prep HPLC to afford 3-((R)-3-((S)-1-(4-(1-isopropyl-6-oxo-1,6-dihydropyridin-3-yl)phenyl)ethyl)-2-oxo-6-phenyl-1,3-oxazinan-6-yl)-2,2-dimethylpropanenitrile (1.99 mg, 30%). LC-MS Method 1 t_R = 2.03 min, m/z = 498; ^1H NMR (CDCl_3) 8.35(d, 1H), 7.80(dd, 1H), 7.37(m, 5H), 7.22(d, 2H), 6.92(d, 2H), 6.83(d, 1H), 5.66(q, 1H), 5.22(m, 1H), 2.93(m, 1H), 2.16(s, 2H), 1.55(d, 3H), 1.46(s, 3H), 1.40(d, 6H), 1.33(s, 3H).

EXAMPLE 75

4108.1002-007 EXAMPLE 674

3-((S)-1-[4-(1-Cyclopropyl-2-oxo-1,2-dihydro-pyridin-4-yl)-phenyl]-ethyl)-(S)-6-(2-hydroxy-2-methyl-propyl)-6-phenyl-[1,3]oxazinan-2-one

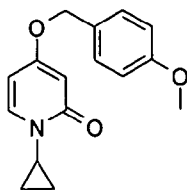
Method 1

2 M aqueous Na_2CO_3 solution (0.23 mL) was added to a solution of (S)-6-(2-hydroxy-2-methylpropyl)-6-phenyl-3-[(S)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl]-1,3-oxazinan-2-one (0.11 g) and trifluoro-methanesulfonic acid 1-cyclopropyl-2-oxo-1,2-dihydro-pyridin-4-yl ester (74 mg; alternatively, 4-bromo-1-cyclopropyl-1H-pyridin-2-one was used) in dimethylformamide (3 mL). The resulting

mixture was sparged with argon for 15 min, before [1,1'-bis(diphenylphosphino)-ferrocene]-dichloropalladium(II) dichloromethane complex (10 mg) was added. The mixture was heated to 100 °C and stirred at this temperature overnight. After cooling to ambient temperature, water was added and the resulting mixture was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried (MgSO₄), and concentrated. The residue was purified by chromatography on silica gel (CH₂Cl₂/MeOH 99:1->90:10) to afford the title compound as a foam-like solid which was crystallized with little ethyl acetate. Yield: 30 mg (27% of theory); Mass spectrum (ESI⁺): m/z = 487 [M+H]⁺.

Intermediate XX

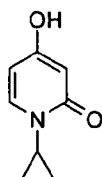
1-Cyclopropyl-4-(4-methoxy-benzyloxy)-1H-pyridin-2-one



A microwave-suited vessel charged with a stir bar, 4-(4-methoxy-benzyloxy)-1H-pyridin-2-one (0.60 g), cyclopropylboronic acid (0.45 g), pyridine (1.50 mL), triethylamine (1.50 mL), and toluene (4 mL) was sparged with argon for 5 min. Then, Cu(OAc)₂ (0.94 g) was added and the mixture was stirred in a microwave oven under microwave irradiation at 140 °C for 45 min. Then, the solvent was evaporated and water was added. The resultant mixture was extracted with ethyl acetate and the combined organic extracts were washed with water and aqueous NaHCO₃ solution. After drying (MgSO₄) and removing the solvent, the residue was purified by chromatography on silica gel (CH₂Cl₂/MeOH 99:1->95:5) to afford the title compound as a solid. Yield: 0.17 g (25% of theory); Mass spectrum (ESI⁺): m/z = 272 [M+H]⁺.

Intermediate XXI

1-Cyclopropyl-4-hydroxy-1H-pyridin-2-one

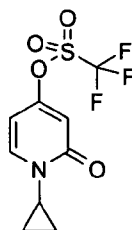


Trifluoroacetic acid (1 mL) was added to a flask charged with a stir bar and 1-cyclopropyl-4-(4-methoxy-benzyloxy)-1H-pyridin-2-one (0.17 g) and chilled in an ice/EtOH bath. The resulting mixture was stirred with cooling for 1.5 h and at ambient temperature for another 4.5 h. Then, the solution was concentrated under reduced pressure and the residue was triturated with tert-butyl methyl ether and dried to give the title compound as a solid. Yield: 0.10 g (quantitative). Mass spectrum (ESI⁺): m/z = 152 [M+H]⁺.

10

Intermediate XXII

Trifluoro-methanesulfonic acid 1-cyclopropyl-2-oxo-1,2-dihydro-pyridin-4-yl ester

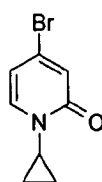


Trifluoromethanesulfonic anhydride (0.12 mL) was added to a flask charged with a stir bar, 1-cyclopropyl-4-hydroxy-1H-pyridin-2-one (0.10 g), NEt₃ (0.24 mL), and dichloromethane (8 mL) and chilled in an ice/EtOH bath. The resulting mixture was stirred with cooling for 2 h and at ambient temperature for another 2 h. Then, the solution was diluted with dichloromethane and washed in succession with water, aqueous NaHCO₃ solution, and water. The organic solution was dried (MgSO₄), the solvent was removed, and the residue was purified by chromatography on silica gel (dichloromethane/methanol 99:1→90:10) to afford the title compound as a resin-like solid. Yield: 0.07 g (36% of theory). Mass spectrum (ESI⁺): m/z = 284 [M+H]⁺.

25

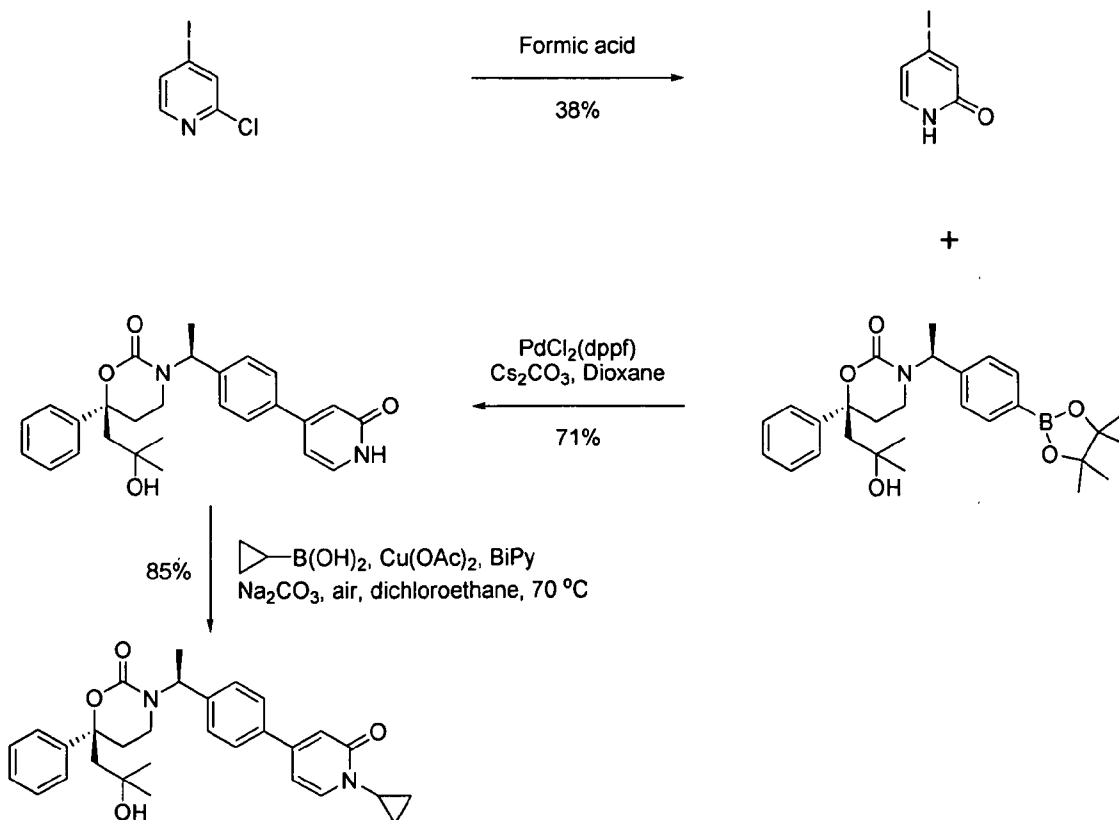
Intermediate XXIII

4-Bromo-1-cyclopropyl-1H-pyridin-2-one



5

Method 2



15

Step 1. 4-Iodopyridin-2(1*H*)-one

A mixture of 2-chloro-4-iodopyridine (4.943 g, 20.6 mmol) and formic acid (88%, 10 mL) was stirred at 105 °C for 21 h. The excess of formic acid was removed in vacuo, and the mixture was quenched with 2 M aq Na₂CO₃, extracted with CH₂Cl₂, dried over Na₂SO₄. After the solvent was removed under reduced pressure, the residue was

5 purified by chromatography on silica gel eluted with CH₂Cl₂/MeOH to afford 1.716 g (38%) of 4-iodopyridin-2(1*H*)-one as a solid. LC-MS Method 1 *t*_R = 0.82 min, *m/z* = 222 (MH⁺); ¹H NMR (400 MHz, (CD₃)₂SO) δ 7.14 (d, *J* = 6.5 Hz, 1H), 6.87 (s, 1H), 6.49 (d, *J* = 7.0 Hz, 1H).

10 Step 2. (S)-6-(2-hydroxy-2-methylpropyl)-3-((S)-1-(4-(2-oxo-1,2-dihydropyridin-4-yl)phenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one

To a solution of (S)-6-(2-hydroxy-2-methylpropyl)-6-phenyl-3-((S)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl)-1,3-oxazinan-2-one (2.646 g, 5.52 mmol) in 1,4-dioxane (60 mL) were added 4-iodopyridin-2(1*H*)-one (1.200 g, 5.43 mmol),

15 2 M Cs₂CO₃ (14.5 mL), and PdCl₂(dppf)·CH₂Cl₂ (0.230 g, 0.28 mmol). The mixture was degassed and heated, under a nitrogen atmosphere, at 120 °C for 15 h. The mixture was diluted with CH₂Cl₂, dried over Na₂SO₄. After the solvents were evaporated, the residue was purified by chromatography on silica gel eluted with MeOH/CH₂Cl₂ to afford

20 1.717 g (71%) of (S)-6-(2-hydroxy-2-methylpropyl)-3-((S)-1-(4-(2-oxo-1,2-dihydropyridin-4-yl)phenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one. LC-MS Method 1 *t*_R = 1.23 min, *m/z* 389, 447 (MH⁺); ¹H NMR (400 MHz, CD₃OD) δ 7.40 (d, *J* = 6.7 Hz, 1H), 7.31 (d, *J* = 8.2 Hz, 2H), 7.29-7.20 (m, 5H), 6.96 (d, *J* = 8.2 Hz, 2H), 6.57-6.52 (m, 2H), 5.49 (q, *J* = 7.0 Hz, 1H), 2.98-2.93 (m, 1H), 2.47-2.34 (m, 2H), 2.16-2.09 (m, 1H), 2.07 (s, 2H), 1.45 (d, *J* = 7.0 Hz, 3H), 1.19 (s, 3H), 0.87 (s, 3H).

25 Step 3. (S)-3-((S)-1-(4-(1-cyclopropyl-2-oxo-1,2-dihydropyridin-4-yl)phenyl)ethyl)-6-(2-hydroxy-2-methylpropyl)-6-phenyl-1,3-oxazinan-2-one

A mixture of (S)-6-(2-hydroxy-2-methylpropyl)-3-((S)-1-(4-(2-oxo-1,2-dihydropyridin-4-yl)phenyl)ethyl)-6-phenyl-1,3-oxazinan-2-one (1.683 g, 3.77 mmol, 1.0 equiv), Cu(OAc)₂

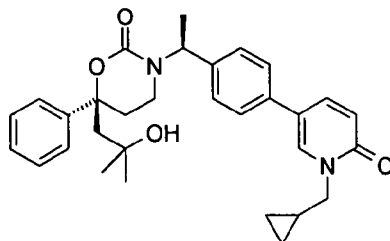
30 (0.692 g, 3.81 mmol, 1.01 equiv), bipyridine (0.599 g, 3.83 mmol, 1.02 equiv), cyclopropylboronic acid (0.681 g, 7.93 mmol, 2.10 equiv) and Na₂CO₃ (0.890 g, 8.40 mmol, 2.23 equiv) in dichloroethane (40 mL) was stirred at 70 °C for 22 h under air. The reaction mixture was quenched with satd aq NH₄Cl, diluted with CH₂Cl₂, dried over

Na₂SO₄. After the solvent was removed under reduced pressure, the residue was purified by chromatography on silica gel eluted with MeOH/CH₂Cl₂ to afford 1.560 g (85%) of (S)-3-((S)-1-(4-(1-cyclopropyl-2-oxo-1,2-dihydropyridin-4-yl)phenyl)ethyl)-6-(2-hydroxy-2-methylpropyl)-6-phenyl-1,3-oxazinan-2-one. LC-MS *t*_R = 1.41 min in 3 min chromatography, *m/z* 429, 487 (MH⁺); ¹H NMR (400 MHz, CD₃OD) δ 7.52 (d, *J* = 7.0 Hz, 1H), 7.29-7.18 (m, 7H), 6.92 (d, *J* = 8.2 Hz, 2H), 6.54 (d, *J* = 1.8 Hz, 1H), 6.47 (dd, *J* = 7.3, 1.8 Hz, 1H), 5.47 (q, *J* = 7.0 Hz, 1H), 3.27-3.21 (m, 1H), 2.95-2.91 (m, 1H), 2.48-2.33 (m, 2H), 2.15-2.08 (m, 1H), 2.07 (s, 2H), 1.42 (d, *J* = 7.0 Hz, 3H), 1.20 (s, 3H), 1.05-1.00 (m, 2H), 0.87 (s, 3H), 0.83-0.79 (m, 2H); ¹³C NMR (100 MHz, CD₃OD) δ 166.17, 155.63, 152.88, 144.03, 142.27, 138.90, 136.91, 129.71, 128.70, 128.58, 127.67, 126.09, 116.08, 107.10, 85.19, 71.49, 55.13, 54.62, 37.44, 33.24, 32.71, 31.86, 30.03, 15.60, 7.27.

EXAMPLE 76

4108.1002-007 EXAMPLE 676

3-((S)-1-[4-(1-Cyclopropylmethyl-6-oxo-1,6-dihydro-pyridin-3-yl)-phenyl]-ethyl)-(S)-6-(2-hydroxy-2-methyl-propyl)-6-phenyl-[1,3]oxazinan-2-one



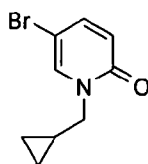
2 M aqueous Na₂CO₃ solution (0.84 mL) was added to a solution of (S)-6-(2-hydroxy-2-methylpropyl)-6-phenyl-3-((S)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl)-1,3-oxazinan-2-one (0.40 g) and 5-bromo-1-cyclopropylmethyl-1H-pyridin-2-one (0.24 g) in dimethyl-formamide (4 mL). The resulting mixture was sparged with argon for 10 min, before [1,1'-bis(diphenylphosphino)ferrocene]-dichloropalladium(II) dichloromethane complex (34 mg) was added. The mixture was heated to 100 °C and stirred at this temperature for 4 h. After cooling to ambient temperature, water was added and the resulting mixture was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried (MgSO₄), and concentrated. The residue was purified by chromatography on silica gel (dichloromethane/methanol 99:1->95:5) to afford the title compound that was crystallized

with little ethyl acetate. Yield: 0.19 g (46% of theory); Mass spectrum (ESI⁺): m/z = 501 [M+H]⁺.

Intermediate XXIV

5

5-Bromo-1-cyclopropylmethyl-1H-pyridin-2-one

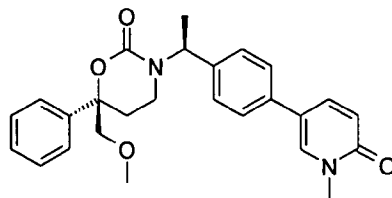


KO^tBu (0.68 g) was added to a solution of 5-bromo-1H-pyridin-2-one (1.00 g) in tetrahydrofuran (20 mL) at room temperature. After stirring for 30 min, cyclopropylmethyl bromide (0.77 mL) and dimethylformamide (3 mL) were added to the suspension and the resulting mixture was warmed to 70 °C. After stirring the mixture at 70 °C for 2 h, the reaction was complete. The mixture was cooled to room temperature, diluted with ethyl acetate (50 mL), and washed with water (2x 20 mL) and brine (20 mL). Then, the solution was dried (MgSO₄) and the solvent was removed to give the title compound as a colorless oil. Yield: 1.18 g (90% of theory). Mass spectrum (ESI⁺): m/z = 228/230 (Br) [M+H]⁺.

EXAMPLE 77

4108.1002-007 EXAMPLE 678

(*R*)-6-Methoxymethyl-3-((*S*)-1-[4-(1-methyl-6-oxo-1,6-dihydro-pyridin-3-yl)-phenyl]-ethyl)-6-phenyl-[1,3]oxazinan-2-one

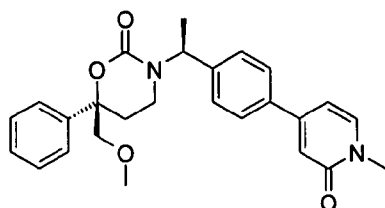


The title compound was prepared from (*R*)-6-(methoxymethyl)-6-phenyl-3-((*S*)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl)-1,3-oxazinan-2-one and 5-bromo-1-methylpyridin-2(1H)-one following a procedure analogous to that described in Example 76. Mass spectrum (ESI⁺): m/z = 433 [M+H]⁺.

EXAMPLE 78

4108.1002-007 EXAMPLE 679

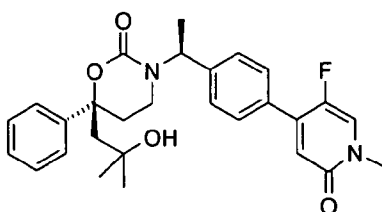
(*R*)-6-Methoxymethyl-3-[(*S*)-1-[4-(1-methyl-2-oxo-1,2-dihydro-pyridin-4-yl)-phenyl]-ethyl]-6-phenyl-[1,3]oxazinan-2-one



The title compound was prepared from (*R*)-6-(methoxymethyl)-6-phenyl-3-[(*S*)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl]-1,3-oxazinan-2-one and trifluoro-methanesulfonic acid 1-methyl-2-oxo-1,2-dihydro-pyridin-4-yl ester following a procedure analogous to that described in Example 76. Mass spectrum (ESI⁺): *m/z* = 433 [M+H]⁺.

EXAMPLE 79

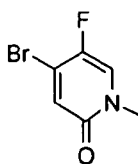
3-[(*S*)-1-[4-(5-Fluoro-1-methyl-2-oxo-1,2-dihydro-pyridin-4-yl)-phenyl]-ethyl]-(*S*)-6-(2-hydroxy-2-methyl-propyl)-6-phenyl-[1,3]oxazinan-2-one



The title compound was prepared from (*S*)-6-(2-hydroxy-2-methylpropyl)-6-phenyl-3-[(*S*)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl]-1,3-oxazinan-2-one and 4-bromo-5-fluoro-1-methyl-1H-pyridin-2-one following a procedure analogous to that described in Example 76. Mass spectrum (ESI⁺): *m/z* = 479 [M+H]⁺.

Intermediate XXV

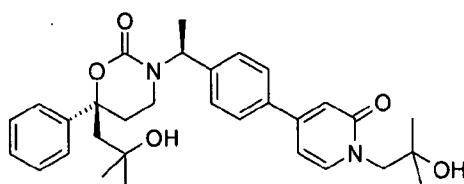
4-Bromo-5-fluoro-1-methyl-1H-pyridin-2-one



Methyl iodide (0.9 mL) was added to a mixture of potassium carbonate (2.34 g) and 4-bromo-5-fluoro-1H-pyridin-2-one (2.50 g) in dimethylformamide (25 mL) at room temperature. The mixture was stirred at room temperature overnight and then water was added. The resulting mixture was extracted with ethyl acetate and the combined extracts were washed with brine and dried (MgSO₄). The solvent was evaporated to afford the crude title compound that was recrystallized from Et₂O. Yield: 1.22 g (45% of theory); Mass spectrum (ESI⁺): m/z = 206/208 (Br) [M+H]⁺.

EXAMPLE 80

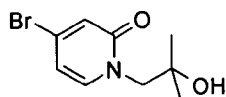
(S)-6-(2-Hydroxy-2-methyl-propyl)-3-((S)-1-{4-[1-(2-hydroxy-2-methyl-propyl)-2-oxo-1,2-dihydro-pyridin-4-yl]-phenyl}-ethyl)-6-phenyl-[1,3]oxazinan-2-one



The title compound was prepared from (S)-6-(2-hydroxy-2-methylpropyl)-6-phenyl-3-[(S)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl]-1,3-oxazinan-2-one and 4-bromo-1-(2-hydroxy-2-methyl-propyl)-1H-pyridin-2-one following a procedure analogous to that described in Example 75. Mass spectrum (ESI⁺): m/z = 519 [M+H]⁺.

Intermediate XXVI

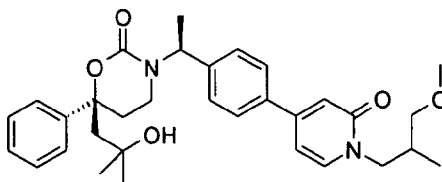
4-Bromo-1-(2-hydroxy-2-methyl-propyl)-1H-pyridin-2-one



A mixture of 4-bromo-1H-pyridin-2-one (0.25 g), 2,2-dimethyl-oxirane (0.26 mL), and potassium carbonate (0.40 g) in dimethylformamide (2.5 mL) was stirred under microwave irradiation at 120 °C for 30 min. After cooling to ambient temperature, the mixture was concentrated and purified by HPLC on reversed phase (acetonitrile/water) to afford the title compound. Yield: 0.34 g (96% of theory); Mass spectrum (ESI⁺): m/z = 246/248 (Br) [M+H]⁺.

EXAMPLE 81

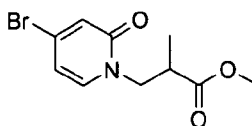
(S)-6-(2-Hydroxy-2-methyl-propyl)-3-((S)-1-{4-[1-(3-methoxy-2-methyl-propyl)-2-oxo-1,2-dihydro-pyridin-4-yl]-phenyl}-ethyl)-6-phenyl-[1,3]oxazinan-2-one



The title compound was prepared from (S)-6-(2-hydroxy-2-methylpropyl)-6-phenyl-3-[(S)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl]-1,3-oxazinan-2-one and 4-bromo-1-(3-methoxy-2-methyl-propyl)-1H-pyridin-2-one following a procedure analogous to that described in Example 75 Method 1. Mass spectrum (ESI⁺): m/z = 533 [M+H]⁺.

Intermediate XXVII

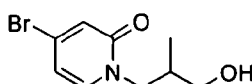
3-(4-Bromo-2-oxo-2H-pyridin-1-yl)-2-methyl-propionic acid methyl ester



A mixture of 4-bromo-1H-pyridin-2-one (0.50 g), methyl 2-bromoisobutyrate (0.45 mL), and potassium carbonate (0.68 g) in dimethylformamide (5 mL) was stirred at 60 °C for 3 h. After cooling to ambient temperature, water was added and the resulting mixture was extracted with ethyl acetate. The combined extracts were washed with brine, dried (MgSO₄), and concentrated. The residue was purified by chromatography on silica gel (cyclohexane/ethyl acetate 70:30->50:50) to afford the title compound. Yield: 0.53 g (67% of theory); Mass spectrum (ESI⁺): m/z = 274/276 (Br) [M+H]⁺. Additionally 2-(4-bromo-pyridin-2-yloxy)-2-methyl-propionic acid methyl ester was obtained {Yield: 0.15 g; Mass spectrum (ESI⁺): m/z = 274/276 (Br) [M+H]⁺}

Intermediate XXVIII

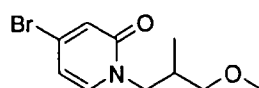
4-Bromo-1-(3-hydroxy-2-methyl-propyl)-1H-pyridin-2-one



LiAlH₄ (1 M solution in tetrahydrofuran, 1.16 mL) was added to a solution of 3-(4-bromo-2-oxo-2H-pyridin-1-yl)-2-methyl-propionic acid methyl ester (0.53 g) in tetrahydrofuran (6 mL) chilled in an ice bath. After stirring the solution with cooling for 2 h, another portion of LiAlH₄ (1 M in tetrahydrofuran, 0.29 mL) was added. After stirring with cooling for 1 more hour, the reaction was quenched by the addition of water. The resulting mixture was extracted with ethyl acetate and the combined organic extracts were washed with brine and dried (MgSO₄). The solvent was evaporated to give the title compound. Yield: 0.37 g (78% of theory); Mass spectrum (ESI⁺): m/z = 246/248 (Br) [M+H]⁺.

Intermediate XXIX

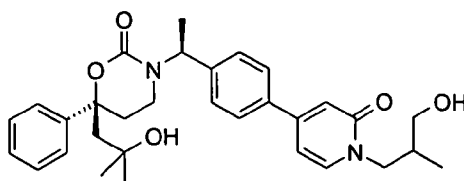
4-Bromo-1-(3-methoxy-2-methyl-propyl)-1H-pyridin-2-one



NaH (60% in mineral oil, 57 mg) was added to a solution of 4-bromo-1-(3-hydroxy-2-methyl-propyl)-1H-pyridin-2-one (0.53 g) in dimethylformamide (6 mL) chilled in an ice bath. After stirring the solution with cooling for 0.5 h, methyl iodide (110 μ L) was added. The cooling bath was removed and the solution was stirred at room temperature overnight. Then, the solution was concentrated under reduced pressure and the residue was diluted with water. The resulting mixture was extracted with ethyl acetate and the combined organic extracts were washed with brine and dried (MgSO₄). The solvent was evaporated and the residue was purified by HPLC on reversed phase (acetonitrile/water) to give the title compound as an oil. Yield: 70 mg (30% of theory); Mass spectrum (ESI⁺): m/z = 260/262 (Br) [M+H]⁺.

EXAMPLE 82

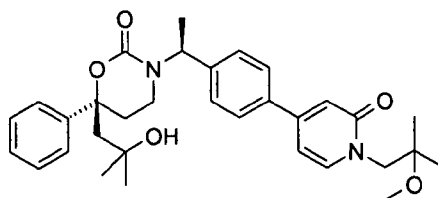
(S)-6-(2-Hydroxy-2-methyl-propyl)-3-((S)-1-(4-[1-(3-hydroxy-2-methyl-propyl)-2-oxo-1,2-dihydro-pyridin-4-yl]-phenyl)-ethyl)-6-phenyl-[1,3]oxazinan-2-one



The title compound was prepared from (S)-6-(2-hydroxy-2-methylpropyl)-6-phenyl-3-[(S)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl]-1,3-oxazinan-2-one and 4-bromo-1-(3-hydroxy-2-methyl-propyl)-1H-pyridin-2-one following a procedure analogous to that described in Example 75. Mass spectrum (ESI⁺): m/z = 519 [M+H]⁺.

EXAMPLE 83

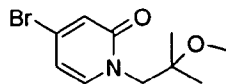
(S)-6-(2-Hydroxy-2-methyl-propyl)-3-(1-{4-[1-(2-methoxy-2-methyl-propyl)-2-oxo-1,2-dihydro-pyridin-4-yl]-phenyl}-ethyl)-6-phenyl-[1,3]oxazinan-2-one



The title compound was prepared from (S)-6-(2-hydroxy-2-methylpropyl)-6-phenyl-3-[(S)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl]-1,3-oxazinan-2-one and 4-bromo-1-(2-methoxy-2-methyl-propyl)-1H-pyridin-2-one following a procedure analogous to that described in Example 75 Method 1. Mass spectrum (ESI⁺): m/z = 533 [M+H]⁺.

Intermediate XXX

4-Bromo-1-(2-methoxy-2-methyl-propyl)-1H-pyridin-2-one



The title compound was prepared from 4-bromo-1-(2-hydroxy-2-methyl-propyl)-1H-pyridin-2-one and methyl iodide following a procedure analogous to that described in Intermediate XXIX. Mass spectrum (ESI⁺): m/z = 260/262 (Br) [M+H]⁺.

BIOLOGICAL TEST EXAMPLE 1

The inhibition of a microsomal preparation of 11 β -HSD1 by compounds of the invention was measured essentially as previously described (K. Solly, S.S. Mundt, H.J. Zokian, G.J. Ding, A. Hermanowski-Vosatka, B. Strulovici, and W. Zheng, High-Throughput Screening of 11-Beta-

Hydroxysteroid Dehydrogenase Type 1 in Scintillation Proximity Assay Format. Assay Drug Dev Technol 3 (2005) 377-384). All reactions were carried out at rt in 96 well clear flexible PET Microbeta plates (PerkinElmer). The assay begins by dispensing 49 μ l of substrate solution (50mM HEPES, pH 7.4, 100mM KCl, 5mM NaCl, 2mM MgCl₂, 2 mM NADPH and 160 nM [³H]cortisone (1 Ci/mmol)) and mixing in 1 μ L of the test compounds in DMSO previously diluted in half-log increments (8 points) starting at 0.1 mM. After a 10 minute pre-incubation, 50 μ L of enzyme solution containing microsomes isolated from CHO cells overexpressing human 11 β -HSD1 (10-20 μ g/ml of total protein) was added, and the plates were incubated for 90 minutes at rt. The reaction was stopped by adding 50 μ l of the SPA beads suspension containing 10 μ M 18 β -glycyrrhetic acid, 5 mg/ml protein A coated YSi SPA beads (GE Healthcare) and 3.3 μ g/ml of anti-cortisol antibody (East Coast Biologics) in Superblock buffer (Bio-Rad). The plates were shaken for 120 minutes at rt, and the SPA signal corresponding to [³H]cortisol was measured on a Microbeta plate reader.

BIOLOGICAL TEST EXAMPLE 2

The inhibition of 11 β -HSD1 by compounds of this invention was measured in whole cells as follows. Cells for the assay were obtained from two sources: fully differentiated human omental adipocytes from Zen-Bio, Inc.; and human omental pre-adipocytes from Lonza Group Ltd. Pre-differentiated omental adipocytes from Zen-Bio Inc. were purchased in 96-well plates and were used in the assay at least two weeks after differentiation from precursor preadipocytes. Zen-Bio induced differentiation of pre-adipocytes by supplementing medium with adipogenic and lipogenic hormones (human insulin, dexamethasone, isobutylmethylxanthine and PPAR-gamma agonist). The cells were maintained in full adipocyte medium (DMEM/Ham's F-12 (1:1, v/v), HEPES pH 7.4, fetal bovine serum, penicillin, streptomycin and Amphotericin B, supplied by Zen-Bio, Inc.) at 37°C, 5% CO₂.

Pre-adipocytes were purchased from Lonza Group Ltd. and placed in culture in Preadipocyte Growth Medium-2 supplemented with fetal bovine serum, penicillin, and streptomycin (supplied by Lonza) at 37°C, 5% CO₂. Pre-adipocytes were differentiated by the addition of insulin, dexamethasone, indomethacin and isobutyl-methylxanthine (supplied by Lonza) to the Preadipocyte Growth Medium-2. Cells were exposed to the differentiating factors for 7 days, at which point the cells were differentiated and ready for the assay. One day before running the assay, the differentiated omental adipocytes were transferred into serum- and phenol-red-free medium for overnight incubation. The assay was performed in a total volume of 200 μ L. The cells were pre-incubated with serum-free, phenol-red-free medium containing 0.1% (v/v) of DMSO and various concentrations of the test compounds at least 1 h before [³H] cortisone in ethanol (50Ci/mmol, ARC, Inc.) was added to achieve a final concentration of cortisone of 100 nM. The cells were incubated for 3-4 hrs at 37°C, 5% CO₂. Negative controls were incubated

without radioactive substrate and received the same amount of [^3H] cortisone at the end of the incubation. Formation of [^3H] cortisol was monitored by analyzing 25 μL of each supernatant in a scintillation proximity assay (SPA). (Solly, K.; Mundt, S. S.; Zokian, H.J.; Ding, G. J.; Hermanowski-Vosatka, A.; Strulovici, B.; Zheng, W. Assay Drug Dev. Technol. 2005, 3, 377-384).

- 5 Many compounds of the invention showed significant activity in this assay.

TABLE OF BIOLOGICAL ASSAY RESULTS

Compound	Biological Test Example 1	
	IC ₅₀ Range ^a	Average % inhibition at 100 nM
EXAMPLE 1	++	90.3
EXAMPLE 2	++	89.1
EXAMPLE 3	++	95.6
EXAMPLE 4	++	95.2
EXAMPLE 5	++	95.6
EXAMPLE 6	++	92.6
EXAMPLE 7	++	75.9
EXAMPLE 8	++	84.5
EXAMPLE 9	++	86.2
EXAMPLE 10	++	95.8
EXAMPLE 11	++	84.1
EXAMPLE 12	++	84.2
EXAMPLE 13	++	90.0
EXAMPLE 14	++	91.0
EXAMPLE 15	++	92.9
EXAMPLE 16	++	95.6
EXAMPLE 17 Isomer 1	++	54.0
EXAMPLE 17 Isomer 2	#	14.8
EXAMPLE 18 Isomer 1	#	23.7

- 161 -

EXAMPLE 18 Isomer 2	++	42.6
EXAMPLE 19	++	36.5
EXAMPLE 20	++	90.9
EXAMPLE 21 Isomer 1	++	103.5
EXAMPLE 21 Isomer 2	++	88.8
EXAMPLE 22 Isomer 1	++	82.5
EXAMPLE 22 Isomer 2	++	88.7
EXAMPLE 23	++	88.2
EXAMPLE 24	++	87.9
EXAMPLE 25	++	93.9
EXAMPLE 26	++	94.7
EXAMPLE 27	++	92.0
EXAMPLE 28 Isomer 1	++	86.9
EXAMPLE 28 Isomer 2	#	42.9
EXAMPLE 29	++	94.1
EXAMPLE 30	++	96.7
EXAMPLE 31	++	90.1
EXAMPLE 32	++	96.4
EXAMPLE 33	++	95.9
EXAMPLE 34	++	95.0
EXAMPLE 35	++	95.8
EXAMPLE 36	++	95.0
EXAMPLE 37	++	96.5
EXAMPLE 38	++	74.3
EXAMPLE 39	++	99.1
EXAMPLE 40	++	95.9
EXAMPLE 41	++	88.7
EXAMPLE 42	++	88.4
EXAMPLE 43	++	96.6

EXAMPLE 44	++	102.0
EXAMPLE 45	++	97.9
EXAMPLE 46	++	94.8
EXAMPLE 47	++	100.1
EXAMPLE 48	++	95.0
EXAMPLE 49	++	97.4
EXAMPLE 50	++	97.1
EXAMPLE 51	++	93.4
EXAMPLE 52	++	95.4
EXAMPLE 53	++	96.6
EXAMPLE 54	++	96.0
EXAMPLE 55	++	96.6
EXAMPLE 56	++	102.8
EXAMPLE 57	++	102.2
EXAMPLE 58	++	104.7
EXAMPLE 59	++	95.9
EXAMPLE 60	++	94.5
EXAMPLE 61	++	96.2
EXAMPLE 62	++	96.9
EXAMPLE 63	++	96.2
EXAMPLE 64	++	94.9
EXAMPLE 65	++	96.1
EXAMPLE 66	++	96.0
EXAMPLE 67	++	97.7
EXAMPLE 68	++	95.6
EXAMPLE 69	++	98.1
EXAMPLE 70	++	96.5
EXAMPLE 71	++	92.2
EXAMPLE 72	++	95.6

- 163 -

EXAMPLE 73	++	99.2
EXAMPLE 74	++	95.0
EXAMPLE 75	++	

^a ++ means IC₅₀ = <100 nM, + means IC₅₀ = 100 – 1000 nM, # means IC₅₀ > 100 nM, - means IC₅₀ > 1000 nM.

5

BIOLOGICAL TEST EXAMPLE 3

In vitro inhibition of 11 β -HSD1 by test compounds was determined with HTRF (Homogeneous Time-Resolved Fluorescence) technology (cisbio international, France) detecting cortisol generated from cortisterone by human liver microsomes. Briefly, compounds were incubated for 1 hour at 37 °C in Tris buffer (20 mM tris, 5 mM EDTA, pH 6.0) containing NADPH (200 μ M) and cortisone (80 nM). Cortisol generated in the reaction is then detected with a competitive immunoassay, involving two HTRF conjugates: cortisol linked to XL665 and anti-cortisol antibody labeled with Europium cryptate. The incubation period for detection reaction was typically 2 hours. The amount of cortisol was determined by reading the time-resolved fluorescence of the wells (Ex 320/75 nm; Em 615/8.5 nm and 665/7.5 nm). The ratio of the two emission signals was then calculated (Em665*10000/Em615). Each assay contained incubations with vehicle controls instead of compound as controls for non-inhibited cortisol generation (100% CTL; 'high values') and incubations with carbenoxolone as controls for fully inhibited enzyme and cortisol background (0% CTL; 'low values'). Each assay also contained a calibration curve with cortisol to transform the fluorescent data into cortisol concentrations. Percent inhibition of each compound was determined relative to the carbenoxolone signal.

In following table the 11 β -HSD 1 inhibitory activities, determined as described above, wherein 100% indicates no inhibition and a value of zero or below zero indicates complete inhibition.

TABLE OF BIOLOGICAL ASSAY RESULTS FOR BIOLOGICAL TEST 3

30

- 164 -

Example	Average %
	control inhibition at 100 nM
75	-14
76	17
77	59
78	58
79	15
80	37
82	-12

BIOLOGICAL TEST EXAMPLE 4

The inhibition of a microsomal preparation of 11 β -HSD1 in the presence of 50% human plasma by compounds of the invention was measured as follows. Microsomes from CHO cells overexpressing human 11 β -HSD1 were diluted into reaction buffer consisting of 25 mM HEPES, pH 7.4, 50 mM KCl, 2.5 mM NaCl, 1 mM MgCl₂, and 50% (v/v) human plasma (BioChemed). The assay began by dispensing 49 μ l of microsome solution into 96-well polypropylene plates and adding 1 μ l of the test compounds in DMSO, previously diluted in half-log increments (8 points) starting at 1.0 mM. The reaction was initiated with the addition of 50 μ l substrate solution consisting of reaction buffer with 2 mM NADPH and 160 nM [³-H]cortisone (1 Ci/mmol). The plates were incubated for 120 minutes at rt, and the reaction was quenched with the addition of 100 μ l acetonitrile with 20 mM cortisone and 20 mM cortisol. After a ten minute incubation at rt, 100 μ l of each well was filtered through a MultiScreen HTS, HV filter plate (Millipore) and diluted with 100 μ l of reaction buffer without human plasma. [³-H]cortisone and [³-H]cortisol were separated by HPLC on a Zorbax SB-C8 column (4.6 x 250 mm, Agilent) with an isocratic elution at 25% acetonitrile in water with 0.01% trifluoroacetic acid, and radioactivity was quantified with an in-line β -RAM (IN/US Systems, Inc.).

TABLE OF BIOLOGICAL ASSAY RESULTS FOR BIOLOGICAL TESTS 1 AND 4

EXAMPLE	Biological Test Example 1 IC ₅₀ (nM)	Biological Test Example 4 ^a IC ₅₀ (nM)	Shift ^b
1	1.51	2.84	1.88
2	0.31	15.54	50.94

4108.1013-001

- 165 -

3	1.59	3.85	2.42
4	1.80	5.60	3.12
5	1.25	3.80	3.04
6	2.36	4.07	1.72
7	35.07	nt	
8	18.33	nt	
9	4.29	13.12	3.06
10	2.91	13.13	4.51
11	5.94	13.51	2.27
12	5.38	31.75	5.90
13	7.22	nt	0.00
14	1.11	2.88	2.59
15	0.58	2.15	3.70
16	0.90	2.00	2.23
17 Isomer 1	75.98	nt	
17 Isomer 2	>100.00	nt	
18 Isomer 1	>100.00	nt	
18 Isomer 2	97.49	nt	
19	95.38	nt	
20	4.28	7.61	1.78
21	3.89	4.72	1.21
21	7.21	9.58	1.33
22 Isomer 1	14.87	75.86	5.10
22 Isomer 2	6.60	20.11	3.05
23	1.99	4.17	2.10
24	3.70	8.28	2.24
25	2.34	5.44	2.32
26	1.49	8.05	5.39
27	3.49	8.41	2.41

4108.1013-001

- 166 -

28 Isomer 1	>100.00	nt	
28 Isomer 2	8.89	nt	
29	1.39	2.76	1.99
30	1.44	3.42	2.37
31	9.01	25.42	2.82
32	3.58	11.48	3.20
33	2.23	3.69	1.66
34	3.19	8.85	2.78
35	2.97	nt	
36	2.03	13.62	6.72
37	1.67	6.44	3.85
38	5.18	nt	
39	1.31	5.10	3.89
40	1.86	7.01	3.77
41	9.28	38.06	4.10
42	6.70	53.38	7.97
43	2.23	3.51	1.57
44	1.08	5.60	5.19
45	1.58	11.85	7.52
46	4.24	16.97	4.00
47	0.96	6.75	7.03
48	1.62	5.54	3.41
49	1.03	2.96	2.86
50	0.61	1.97	3.23
51	5.46	7.89	1.45
52	3.24	14.09	4.35
53	1.35	4.19	3.10
54	2.40	7.05	2.94
55	1.66	7.18	4.31

- 167 -

56	1.03	13.19	12.81
57	1.26	12.45	9.92
58	0.87	8.98	10.32
59	1.53	4.02	2.63
60	0.75	7.00	9.40
61	1.40	6.99	4.99
62	2.48	11.96	4.82
63	3.85	102.97	26.73
64	1.64	9.62	5.87
65	0.80	4.64	5.82
66	1.47	6.71	4.58
67	2.01	7.29	3.63
68	0.96	4.39	4.59
69	0.72	3.89	5.42
70	1.01	2.63	2.60
71	0.65	3.96	6.09
72	4.04	8.23	2.04
73	1.99	33.08	16.62
74	1.21	8.76	7.24
75	1.40	2.80	2.00

^a nt means not tested; ^b Shift is the IC₅₀ determined in Biological Test Example 4 divided by the IC₅₀ determined in Biological Test Example 1.

TABLE OF BIOLOGICAL ASSAY RESULTS FOR COMPARATOR COMPOUNDS IN
BIOLOGICAL TESTS 1 AND 4

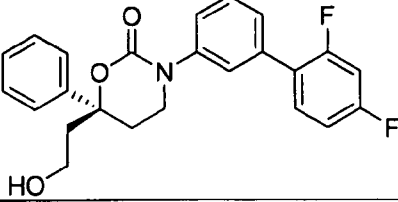
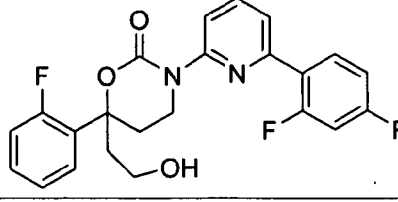
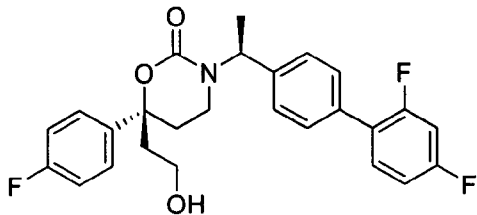
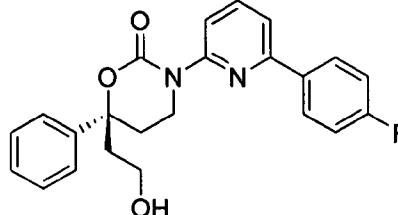
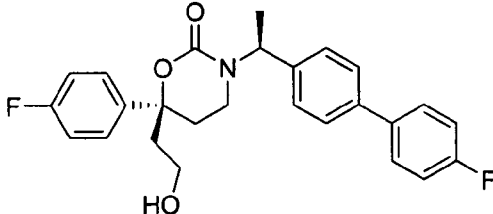
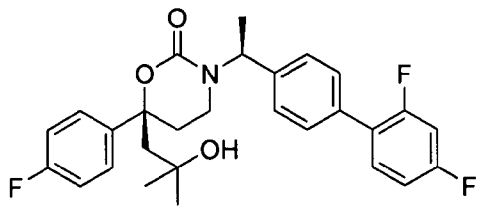
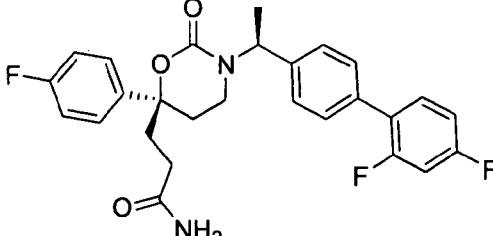
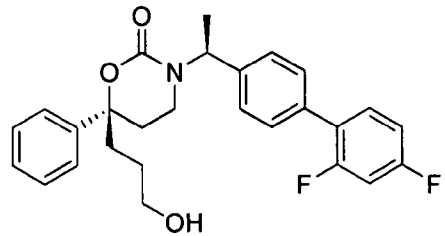
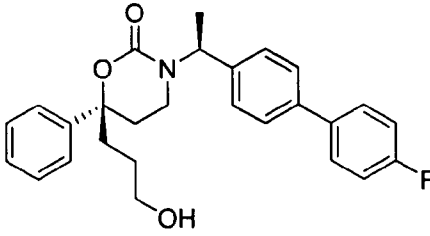
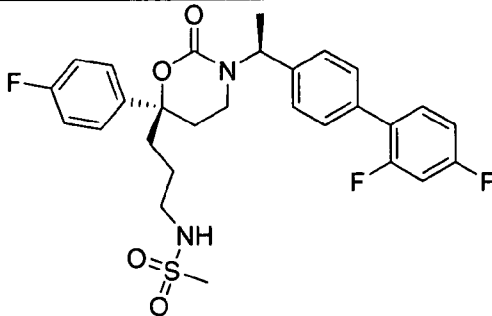
5

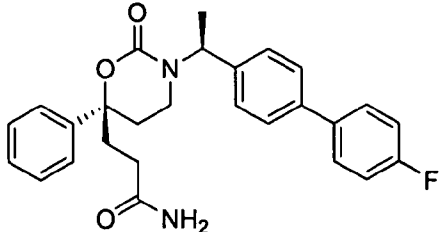
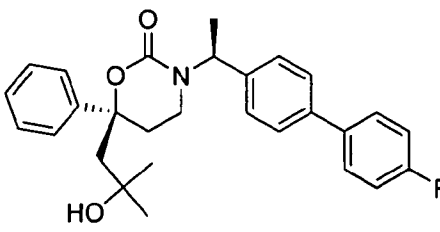
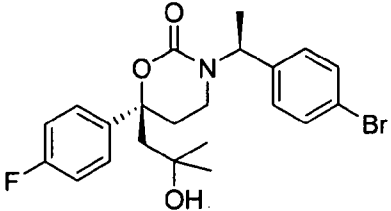
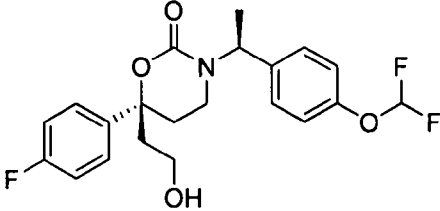
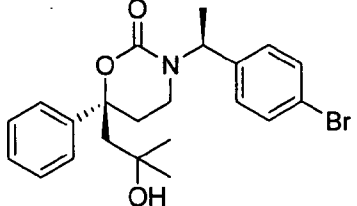
Comparator Compound	Biological Test Example 1 IC ₅₀ (nM)	Biological Test Example 4 ^a IC ₅₀ (nM)	Shift ^b
1	0.77	11.97	15.51
2	1.80	14.16	7.88

- 168 -

3	0.75	17.74	23.63
4	1.44	15.24	10.57
5	0.51	18.50	36.10
6	1.48	37.58	25.39
7	0.99	41.90	42.43
8	0.72	17.85	24.74
9	0.55	11.86	21.45
10	1.79	53.49	29.91
11	0.55	13.40	24.59
12	1.08	19.54	18.12
13	0.76	6.32	8.30
14	1.30	8.94	6.90
15	0.79	8.94	11.32

^a nt means not tested; ^b Shift is the IC₅₀ determined in Biological Test Example 4 divided by the IC₅₀ determined in Biological Test Example 1.

 Comparator 1	 Comparator 2
 Comparator 3	 Comparator 4
 Comparator 5	 Comparator 6
 Comparator 7	 Comparator 8
 Comparator 9	 Comparator 10

	
Comparator 11	Comparator 12
	
Comparator 13	Comparator 14
	
Comparator 15	

The compounds of the invention are useful for ameliorating or treating disorders
 5 or diseases in which decreasing the level of cortisol is effective in treating a disease
 state. Thus, the compounds of the invention can be used in the treatment or prevention
 of diabetes mellitus (e.g., type II diabetes) , obesity, symptoms of metabolic syndrome,
 glucose intolerance, hyperglycemia, hypertension, hyperlipidemia, insulin resistance,
 cardiovascular disease, dyslipidemia, atherosclerosis, lipodystrophy, osteoporosis,
 10 glaucoma, Cushing's syndrome, Addison's Disease, visceral fat obesity associated with
 glucocorticoid therapy, depression, anxiety, Alzheimer's disease, dementia, cognitive
 decline (including age-related cognitive decline), polycystic ovarian syndrome, infertility
 and hypergonadism. The compounds of the invention can be used as therapeutic
 agents for pseudo Cushing's Syndrome associated with alcoholic liver disease. In
 15 addition, the compounds modulate the function of B and T cells of the immune system
 and can therefore be used to treat diseases such as tuberculosis, leprosy and psoriasis.
 They can also be used to promote wound healing, particularly in diabetic patients.

Additional diseases or disorders that are related to 11 β -HSD1 activity include
 those selected from the group consisting of lipid disorders, hypertriglyceridemia,

hypercholesterolemia, low HDL levels, high LDL levels, vascular restenosis, pancreatitis, abdominal obesity, neurodegenerative disease, retinopathy, nephropathy, neuropathy, diabetes, coronary heart disease, stroke, peripheral vascular disease, Cushing's syndrome, hyperinsulinemia, viral diseases, and Syndrome X. A further disease related to 11 β -HSD1 activity is pseudo Cushing's Syndrome associated with alcoholic liver disease.

A pharmaceutical composition of the invention may, alternatively or in addition to an 11 β -HSD1 inhibitor of the invention, comprise a pharmaceutically acceptable salt of a an 11 β -HSD1 inhibitor of the invention and one or more pharmaceutically acceptable carriers therefore. Alternatively, a pharmaceutical composition of the invention may comprise a compound of an 11 β -HSD1 inhibitor of the invention or a pharmaceutical salt thereof as the only pharmaceutically active agent in the pharmaceutical composition. The disclosed 11 β -HSD1 inhibitors can be used alone or in a combination therapy with one or more additional agents for the treatment of diabetes, dyslipidemia, cardiovascular disease, hypertension, obesity, cancer or glaucoma.

The compositions of the invention are 11 β -HSD1 inhibitors. Said compositions contain compounds having a mean inhibition constant (IC₅₀) against 11 β -HSD1 of below about 1,000 nM; preferably below about 100 nM; more preferably below about 50 nM; even more preferably below about 5 nM; and most preferably below about 1 nM.

The invention includes a therapeutic method for treating or ameliorating an 11 β -HSD1 mediated disorder in a subject in need thereof comprising administering to a subject in need thereof an effective amount of an 11 β -HSD1 inhibitor of the invention, or an enantiomer, diastereomer, or pharmaceutically acceptable salt thereof or composition thereof. 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.

An embodiment of the invention includes administering an 11 β -HSD1 inhibiting compound of the invention or composition thereof in a combination therapy with one or more additional agents for the treatment of diabetes, dyslipidemia, cardiovascular

disease, hypertension, obesity, cancer or glaucoma. Agents for the treatment of diabetes include insulins, such as Humulin® (Eli Lilly), Lantus® (Sanofi Aventis), Novolin (Novo Nordisk), and Exubera® (Pfizer); PPAR gamma agonists, such as Avandia® (rosiglitazone maleate, GSK) and Actos® (pioglitazone hydrochloride, Takeda/Eli Lilly);
5 sulfonyleureas, such as Amaryl® (glimepiride, Sanofi Aventis), Diabeta® (glyburide, Sanofi Aventis), Micronase®/Glynase® (glyburide, Pfizer), and Glucotrol®/Glucotrol XL® and (glipizide, Pfizer); meglitinides, such as Prandin®/NovoNorm® (repaglinide, Novo Nordisk), Starlix® (nateglinide, Novartis), and Glufast® (mitiglinide, Takeda); biguanides, such as Glucophage®/Glucophage XR® (metformin HCl, Bristol Myers Squibb) and
10 Glumetza (metformin HCl, Depomed); thiazolidinediones; amylin analogs, GLP-1 analogs; DPP-IV inhibitors; PTB-1B inhibitors; protein kinase inhibitors (including AMP-activated protein kinase inhibitors); glucagon antagonists, glycogen synthase kinase-3 beta inhibitors; glucose-6-phosphatase inhibitors; glycogen phosphorylase inhibitors; sodium glucose co-transporter inhibitors, and alpha-glucosidase inhibitors, such as
15 Precose®/Glucobay®/Prandase®/Glucor® (acarbose, Bayer) and Glyset® (miglitol, Pfizer). Agents for the treatment of dyslipidemia and cardiovascular disease include statins, fibrates, and ezetimibe. Agents for the treatment of hypertension include alpha-blockers, beta-blockers, calcium channel blockers, diuretics, angiotensin converting enzyme (ACE) inhibitors, dual ACE and neutral endopeptidase (NEP) inhibitors,
20 angiotensin-receptor blockers (ARBs), aldosterone synthase inhibitors, aldosterone-receptor antagonists, or endothelin receptor antagonist. Agents for the treatment of obesity include orlistat, phentermine, sibutramine and rimonabant.

An embodiment of the invention includes administering an 11 β -HSD1 inhibiting compound of the invention or composition thereof in a combination therapy with one or
25 more other 11 β -HSD1 inhibitors, or with combination products, such as Avandamet® (metformin HCl and rosiglitazone maleate, GSK); Avandaryl® (glimepiride and rosiglitazone maleate, GSK); Metaglip® (glipizide and metformin HCl, Bristol Myers Squibb); and Glucovance® (glyburide and metformin HCl, Bristol Myers Squibb).

The compounds of the present invention can be prepared and administered in a
30 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.

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, 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.

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.

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 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.

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, capsule, or lozenge itself, or it can be the appropriate amount of any of these in packaged form.

The quantity of active ingredient in a unit dose preparation may be varied or adjusted from about 0.1 mg to about 1000.0 mg, preferably from about 0.1 mg to about 100 mg. The dosages, however, 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 art. Also, the pharmaceutical composition may contain, if desired, other compatible therapeutic agents.

In therapeutic treatment or as a method-of-use as an inhibitor of 11 β -HSD1 or an inhibitor in the production of cortisol in the cell, the active ingredient is preferably administered orally in a solid dosage form as disclosed above in an amount of about 0.1 mg to about 100 mg per daily dose where the dose is administered once or more than once daily.

All publications, patents and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication or patent application were specifically and individually designated as having been incorporated by reference. It is understood that the examples and embodiments described herein are for illustrative purposes only, and it will be appreciated that the invention is susceptible to modification, variation and change without departing from the proper scope or fair meaning of the appended claims.

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.

ABSTRACT

This invention relates to novel compounds of the Formula Ik, Im¹, Im², Im⁵, In¹, In², In⁵, Io¹, Io², Io⁵, Ip¹, Ip³, pharmaceutically acceptable salts thereof, and pharmaceutical
5 compositions thereof, which are useful for the therapeutic treatment of diseases associated with the modulation or inhibition of 11 β -HSD1 in mammals. The invention further relates to pharmaceutical compositions of the novel compounds and methods for their use in the reduction or control of the production of cortisol in a cell or the inhibition of the conversion of cortisone to cortisol in a cell.