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1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-amino-3-tiabiciclo[3.1.0]hexan-6-il]piridina-5-il]-3-fluorofenil]-2-oxooxazolidin-5-ilmetil]-1,2,3-triazol S-óxido,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-t-butoxicarbonilamino-3-tiabiciclo[3.1.0]hexan-6-il]piridina-5-il]-3-fluorofenil]-2-oxooxazolidin-5-ilmetil]-1,2,3-triazol S,S-dióxido,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-amino-3-tiabiciclo[3.1.0]hexan-6-il]piridina-5-il]-3-fluorofenil]-2-oxooxazolidin-5-ilmetil]-1,2,3-triazol S,S-dióxido,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-t-butoxicarbonilamino-3-tiabiciclo[3.1.0]hexan-6-il]piridina-5-il]-3,5-difluorofenil]-2-oxooxazolidin-5-ilmetil]-1,2,3-triazol,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-amino-3-tiabiciclo[3.1.0]hexan-6-il]piridina-5-il]-3,5-difluorofenil]-2-oxooxazolidin-5-ilmetil]-1,2,3-triazol,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-t-butoxicarbonilamino-3-tiabiciclo[3.1.0]hexan-6-il]piridina-5-il]-3,5-difluorofenil]-2-oxooxazolidin-5-ilmetil]-1,2,3-triazol S-óxido,

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1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-amino-3-tiabiciclo[3.1.0]hexan-6-il]piridina-5-il]-3,5-difluorofenil]-2-oxooxazolidin-5-ilmetil]-1,2,3-triazol S-óxido,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-t-butoxicarbonilamino-3-tiabiciclo[3.1.0]hexan-6-il]piridina-5-il]-3,5-difluorofenil]-2-oxooxazolidin-5-ilmetil]-1,2,3-triazol S,S-dióxido,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-amino-3-tiabiciclo[3.1.0]hexan-6-il]piridina-5-il]-3,5-difluorofenil]-2-oxooxazolidin-5-ilmetil]-1,2,3-triazol S,S-dióxido,

5(R)-3-[4-[2-[(1α,5α,6β)-3-t-butoxicarbonil-6-Ciano-3-azabiciclo[3.1.0]hexan-6-il]piridina-5-il]-3,5-difluorofenil]-5-[(isoxazol-3-il)oxi]metiloxazolidin-2-ona,

5(R)-3-[4-[2-[(1α,5α,6β)-6-Ciano-3-azabiciclo[3.1.0]hexan-6-il]piridina-5-il]-3,5-difluorofenil]-5-[(isoxazol-3-il)oxi]metiloxazolidin-2-ona,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-Ciano-3-(4-metilpiperazin-1-il)acetil-3-azabiciclo[3.1.0]hexan-6-il]piridina-5-il]-3-fluorofenil]-2-oxooxazolidin-5-ilmetil]-1,2,3-triazol,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-Ciano-3-tiabiciclo[3.1.0]hexan-6-il]piridina-5-il]fenil]-2-oxooxazolidin-5-ilmetil]-1,2,3-triazol,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-Ciano-3-tiabiciclo[3.1.0]hexan-6-il]piridina-5-il]fenil]-2-oxooxazolidin-5-ilmetil]-1,2,3-triazol S-óxido,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-Ciano-3-tiabiciclo[3.1.0]hexan-6-il]piridina-5-il]fenil]-2-oxooxazolidin-5-ilmetil]-1,2,3-triazol S,S-dióxido,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-Ciano-3-tiabiciclo[3.1.0]hexan-6-il]piridina-5-il]-3,5-difluorofenil]-2-oxooxazolidin-5-ilmetil]-1,2,3-triazol,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-Ciano-3-tiabiciclo[3.1.0]hexan-6-il]piridina-5-il]-3,5-difluorofenil]-2-oxooxazolidin-5-ilmetil]-1,2,3-triazol S-óxido,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-Ciano-3-tiabiciclo[3.1.0]hexan-6-il]piridina-5-il]-3,5-difluorofenil]-2-oxooxazolidin-5-ilmetil]-1,2,3-triazol S,S-dióxido,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-Ciano-3-(1,3-diacetoxipropan-2-il)-3-azabiciclo[3.1.0]hexan-6-il]piridina-5-il]-3-fluorofenil]-2-oxooxazolidin-5-ilmetil]-1,2,3-triazol,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-3-[(3R,4S)-1-azabiciclo[2.2.1]hepan-3-il]carbonil-6-Ciano-3-azabiciclo[3.1.0]hexan-6-il]piridina-5-il]-3-fluorofenil]-2-oxooxazolidin-5-ilmetil]-1,2,3-triazol,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-Ciano-3-(piridina-2-il)-3-azabiciclo[3.1.0]hexan-6-il]piridina-5-il]-3-fluorofenil]-2-oxooxazolidin-5-ilmetil]-1,2,3-triazol,

5(R)-3-[4-[2-[(1α,5α,6β)-3-t-butoxicarbonil-6-Ciano-3-azabiciclo[3.1.0]hexan-6-il]piridina-5-il]-3,5-difluorofenil]-5-[N-(t-butoxicarbonil)-N-(isoxazol-3-il)]aminometiloxazolidin-2-ona,

5(R)-3-[4-[2-[(1α,5α,6β)-6-Ciano-3-azabiciclo[3.1.0]hexan-6-il]piridina-5-il]-3,5-difluorofenil]-5-[N-(isoxazol-3-il)]aminometiloxazolidin-2-ona,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-Ciano-3-(tiatriazol-2-il)-3-azabiciclo[3.1.0]hexan-6-il]piridina-5-il]-3-fluorofenil]-2-oxooxazolidin-5-ilmetil]-1,2,3-triazol,

N-[5(S)-3-[4-[2-[(1α,5α,6β)-3-t-butoxicarbonil-6-Ciano-3-azabiciclo[3.1.0]hexan-6-il]piridina-5-il]-3-fluorofenil]-2-oxooxazolidin-5-ilmetil]tioacetamida,

N-[5(S)-3-[4-[2-[(1α,5α,6β)-6-Ciano-3-azabiciclo[3.1.0]hexan-6-il]piridina-5-il]-3-fluorofenil]-2-oxooxazolidin-5-ilmetil]tioacetamida,

N-[5(S)-3-[4-[2-[(1α,5α,6β)-3-t-butoxicarbonil-6-Ciano-3-azabiciclo[3.1.0]hexan-6-il]piridina-5-il]-3-fluorofenil]-2-oxooxazolidin-5-ilmetil]isotiocianato,

O-metil-N-[5(S)-3-[4-[2-[(1α,5α,6β)-3-t-butoxicarbonil-6-Ciano-3-azabiciclo[3.1.0]hexan-6-il]- piridina-5-il]-3-fluorofenil]-2-oxooxazolidin-5-ilmetil] tiocarbamato,

O-metil-N-[5(S)-3-[4-[2-[(1α,5α,6β)-6-Ciano-3-azabiciclo[3.1.0]hexan-6-il]piridina-5-il]-3-fluorofenil]-2-oxooxazolidin-5-ilmetil]tiocarbamato,

o su enantiomero, diastereomero, o sal farmacéuticamente aceptable, hidrato o prodroga de los mismos.

11 Un compuesto de acuerdo con la reivindicación 10, que es,

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1-[5(R)-3-[4-[4-[(1α,5α,6β)-6-Ciano-3-azabiciclo[3.1.0]hexan-6-il]-3-fluorofenil]-3-fluorofenil]-2-oxooxazolidin-5-ilmetil]-1,2,3-triazol,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-Ciano-3-azabiciclo[3.1.0]hexan-6-il]piridina-5-il]-3-fluorofenil]-2-oxooxazolidin-5-ilmetil]-1,2,3-triazol,

N-[5(S)-3-[4-[4-[(1α,5α,6β)-6-Ciano-3-azabiciclo[3.1.0]hexan-6-il]-3-fluorofenil]fenil]-2-oxooxazolidin-5-ilmetil]acetamida,

N-[5(S)-3-[4-[2-[(1α,5α,6β)-6-Ciano-3-azabiciclo[3.1.0]hexan-6-il]piridina-5-il]fenil]-2-oxooxazolidin-5-ilmetil]acetamida,

N-[5(S)-3-[4-[2-[(1α,5α,6β)-6-Ciano-3-azabiciclo[3.1.0]hexan-6-il]-3-fluorofenil]-3-fluorofenil]-2-oxooxazolidin-5-ilmetil]acetamida,

N-[5(S)-3-[4-[2-[(1α,5α,6β)-6-Ciano-3-azabiciclo[3.1.0]hexan-6-il]piridina-5-il]-3-fluorofenil]-2-oxooxazolidin-5-ilmetil]acetamida,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-Amino-3-oxabiciclo[3.1.0]hexan-6-il]piridina-5-il]-3-fluorcfenil]-2-oxooxazolidin-5-ilmetil]-1,2,3-triazol,

1-[5(R)-3-[3-Fluoro-4-[2-(1-metiltetrazol-5-il)piridina-5-il]fenil]-2-oxooxazolidin-5-ilmetil]-1,2,3-triazol,

1-[5(R)-3-[4-[4-[(1α,5α,6β)-6-Ciano-3-azabiciclo[3.1.0]hexan-6-il]-3,5-difluorofenil]-3-fluorofenil]-2-oxooxazolidin-5-ilmetil]-1,2,3-triazol,

N-[5(S)-3-[4-[4-[(1α,5α,6β)-6-Ciano-3-azabiciclo[3.1.0]hexan-6-il]piridina-5-il]-3,5-difluorofenil]-2-oxooxazolidin-5-ilmetil]acetamida,

N-[5(S)-3-[4-[4-[(1α,5α,6β)-6-Ciano-3-azabiciclo[3.1.0]hexan-6-il]-3,5-difluorofenil]-3-fluorofenil]-2-oxooxazolidin-5-ilmetil]acetamida,

N-[5(S)-3-[4-[4-[(1α,5α,6β)-6-Ciano-3-azabiciclo[3.1.0]hexan-6-il]fenil]-3-fluorofenil]-2-oxooxazolidin-5-ilmetil]acetamida,

1-[5(R)-3-[4-[4-[(1α,5α,6β)-6-Ciano-3-azabiciclo[3.1.0]hexan-6-il]fenil]-3-fluorofenil]-2-oxooxazolidin-5-ilmetil]-1,2,3-triazol,

4-[5(R)-3-[4-[2-[(1α,5α,6β)-6-Ciano-3-azabiciclo[3.1.0]hexan-6-il]piridina-5-il]-3-fluorofenil]-2-oxooxazolidin-5-ilmetil]-1,2,4-triazol,

5(R)-3-[4-[2-[(1α,5α,6β)-6-Ciano-3-azabiciclo[3.1.0]hexan-6-il]piridina-5-il]-3-fluorofenil]-5-[(isoxazol-3-il)oxi]metiloxazolidin-2-ona,

5(R)-3-[4-[2-[(1α,5α,6β)-6-Ciano-3-azabiciclo[3.1.0]hexan-6-il]piridina-5-il]-3-fluorofenil]-5-[N-(isoxazol-3-il)]aminometiloxazolidin-2-ona,

N-[5(S)-3-[4-[2-[(1α,5α,6β)-6-Ciano-3-azabiciclo[3.1.0]hexan-6-il]piridina-5-il]-3-fluorofenil]-2-oxooxazolidin-5-ilmetil]ciclopropanocarboxamida,

N-[5(S)-3-[4-[2-[(1α,5α,6β)-6-Ciano-3-azabiciclo[3.1.0]hexan-6-il]piridina-5-il]-3-fluorofenil]-2-oxooxazolidin-5-ilmetil]difluoroacetamida,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-3-[(1-Aminociclopropan-1-il)carbonil]-6-Ciano-3-azabiciclo[3.1.0]hexan-6-il]piridina-5-il]-3-fluorofenil]-2-oxooxazolidin-5-ilmetil]-1,2,3-triazol,

o su enantiomero, diastereomero, o sal farmacéuticamente aceptable, hidrato o prodroga de los mismos.

12. El compuesto de acuerdo con la reivindicación 11, que es:

clorohidrato de 1-[5(R)-3-[4-[4-[(1α,5α,6β)-6-Ciano-3-azabiciclo[3.1.0]hexan-6-il]-3-fluorofenil]-3-fluorofenil]-2-oxooxazolidin-5-ilmetil]-1,2,3-triazol,

clorohidrato de 1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-Ciano-3-azabiciclo[3.1.0]hexan-6-il]piridina-5-il]-3-fluorofenil]-2-oxooxazolidin-5-ilmetil]-1,2,3-triazol,

clorohidrato de N-[5(S)-3-[4-[4-[(1α,5α,6β)-6-Ciano-3-azabiciclo[3.1.0]hexan-6-il]-3-fluorofenil]fenil]-2-oxooxazolidin-5-ilmetil]acetamida,

clorohidrato de N-[5(S)-3-[4-[2-[(1α,5α,6β)-6-Ciano-3-azabiciclo[3.1.0]hexan-6-il]piridina-5-il]fenil]-2-oxooxazolidin-5-ilmetil]acetamida,

clorohidrato de N-[5(S)-3-[4-[2-[(1α,5α,6β)-6-Ciano-3-azabiciclo[3.1.0]hexan-6-il]-3-fluorofenil]-3-fluorofenil]-2-oxooxazolidin-5-ilmetil]acetamida, o

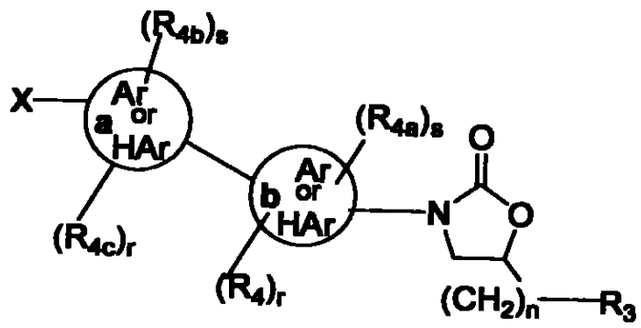
Clorohidrato de N-[5(S)-3-[4-[2-[(1α,5α,6β)-6-Ciano-3-azabiciclo[3.1.0]hexan-6-il]piridina-5-il]-3-fluorofenil]-2-oxooxazolidin-5-ilmetil]acetamida.

13. Una composición farmacéutica compuesta por un compuesto de acuerdo con la reivindicación 1 en combinación con un portador farmacéuticamente aceptable, dicha composición opcionalmente en combinación con una vitamina seleccionada del grupo formado por vitamina B2, vitamina B6, vitamina B12 y acido fólico.

14. Un método para tratar o prevenir una infección bacterial o un efecto colateral asociado con oxazolidina en un paciente mamifero que necesita dicha compuesto que comprende administrar a un paiente una cantidad efectiva del compuesto de la reivindicación 1 y opcionalmente una cantidad efectiva de una o más vitaminas seleccionadas del grupo formado por vitamina B2, vitamina B6, vitamina B12 y ácido fólico a un paciente que las necesita.

15. Un método de acuerdo con la reivindicación 14, caracterizado porque el efecto colateral asociado con la

oxazolidinona es anemia normocítica, anemia sideroblástica, neuropatía sensorial periférica, neuropatía óptica, apoplegía, trombocitopenia, queilosis, dermatitis seborreica, anemia hiporregenerativa o anemia megaloblástica.


(R4b)s
X
Ar
or
a
HAr
(R4c)r
(R4)r
Ar
or
b
HAr
(R4a)s
O
N
O
(CH2)n
R3

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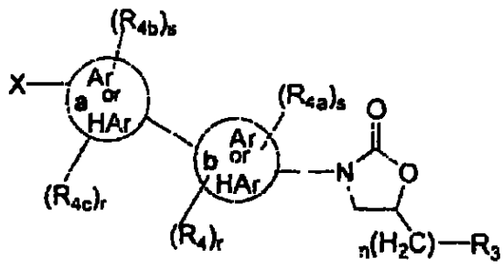

(I)

(57) Abstract: This invention relates to new oxazolidinones having a cyclopropyl moiety which are effective against aerobic and anaerobic pathogens such as multi-resistant staphylococci, streptococci and enterococci, Bacteroides spp., Clostridia spp. and as well as acid-fast organisms such as *Mycobacterium tuberculosis* and other mycobacterial species. The compounds are represented by structural formula (I) or its enantiomer, diastereomer, or pharmaceutically acceptable salt or ester thereof.

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SUPERINDUSTRIA Y COMERCIO
Radicacion : 05131137
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Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE [3]

	USUARIO	RADICADOR
PATENTE DE INVENCIÓN ✓ MODELO DE UTILIDAD	( )	( )
- Indicación de que se solicita la concesión de una patente. ✓	( )	( )
- Datos de identificación del solicitante o de la persona que se presenta la solicitud. ✓	( )	( )
- Descripción de la invención ✓	( )	( )
- Dibujos de ser estos pertinentes ✓	( )	( )
- Comprobante de Pago de las tasas establecidas. ✓	( )	( )
COMPLETA ( ) INCOMPLETA	( )	( )
DISEÑO INDUSTRIAL ( )		
- Indicación de que se solicita el registro de Diseño Industrial	( )	( )
- Datos de identificación del solicitante o de la persona que presenta la solicitud.	( )	( )
- Representación gráfica o fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño.	( )	( )
Comprobante de pago de las tasas establecidas	( )	( )
COMPLETA ( ) INCOMPLETA	( )	( )
ESQUEMA DE TRAZADO ( )		
- Indicación de que solicita el registro de un Esquema de trazado.	( )	( )
- Datos de identificación del solicitante o de la persona que presenta La solicitud.	( )	( )
Representación gráfica del esquema de trazado	( )	( )
Comprobante de pago de las tasas establecidas.	( )	( )
COMPLETA ( ) INCOMPLETA	( )	( )

Firma Responsable:

Fecha: Dic 29 de 2005

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INTERNATIONAL PATENT AND TRADEMARK OFFICE

Trademark	Marcas
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Health Permit	Registros Sanitarios
Software	Soporte Lógico
Commercial Name	Nombres Comerciales
Design	Diseños

Señores
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
E. S. D.

REF: EXPEDIENTE: 05-131137
PATENTE DE INVENCION PCT: "ANTIBIÓTICOS DE OXAZOLIDINONA SUSTITUIDOS CON UN GRUPO CICLOPROPILO Y DERIVADOS DE..."

Estimados señores:

Damos alcance a la solicitud de patente PCT Fase nacional presentada ante su Despacho y radicada el día 29 de diciembre del 2005 según expediente citado en la referencia, con el fin de presentar copias de los siguientes documentos expedidos según el Tratado en Materia de Cooperación de Patentes:

1. Copia de la publicación internacional No. WO 2005/005398 A2 de la patente PCT/US2004/020734, con su respectiva traducción al español.
2. Carta remisoria de pedido solicitando que la solicitud internacional siga el proceso de acuerdo con formulario PCT/RO/101, con su traducción al español.
3. Copia del formulario de notificación concerniente al pago de los aranceles previstos (PCT, cláusulas PCT/ISA/206
4. Carta de respuesta a la invitación para pagar aranceles adicionales, con su traducción al español.
5. Copia del Formulario de transmisión de informe de búsqueda internacional y de la Opinión escrita de la autoridad de búsqueda internacional, con su traducción al español, formulario PCT/ISA/220 y 210 y 237.
6. Carta de respuesta a la opinión Escrita, junto con su traducción al español.
7. Copia del formulario de acuse de recibo de copia de archivo de presentación de la solicitud internacional, Formulario PCT/IB/301.
8. Copia del formulario de Notificación para informar al solicitante sobre la comunicación de la solicitud internacional a las oficinas designadas, con su traducción al español, Formulario PCT/IB/308.

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Del señor Jefe

CARLOS ORLANDO MAYA RODRIGUEZ
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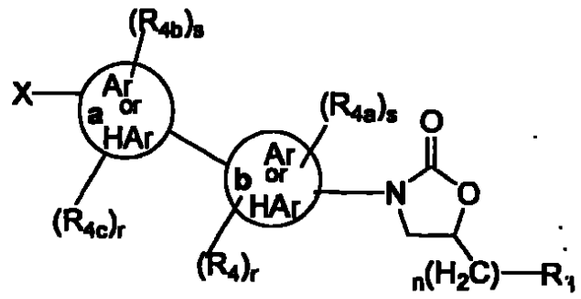

(I)

(57) Abstract: This invention relates to new oxazolidinones having a cyclopropyl moiety, which are effective against aerobic and anerobic pathogens such as multi-resistant staphylococci, streptococci and enterococci, Bacteroides spp., Clostridia spp. species, as well as acid-fast organisms such as *Mycobacterium tuberculosis* and other mycobacteria species. The compounds are represented by structural formula: (I): its enantiomer, diastereomer, or pharmaceutically acceptable salt or ester thereof.

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CYCLOPROPYL GROUP SUBSTITUTED OXAZOLIDINONE ANTIBIOTICS AND DERIVATIVES THEREOF

Cross Reference to Related Applications

This application claims the benefit of U.S. Provisional Application No. 60/483,904, filed July 2, 2003, entitled CYCLOPROPYL GROUP SUBSTITUTED OXAZOLIDINONE ANTIBIOTICS AND DERIVATIVES THEREOF, and U.S. Provisional Application 60/546,984, filed February 24, 2004, entitled CYCLOPROPYL GROUP SUBSTITUTED OXAZOLIDINONE ANTIBIOTICS AND DERIVATIVES THEREOF, which are hereby incorporated herein by reference it their entirety.

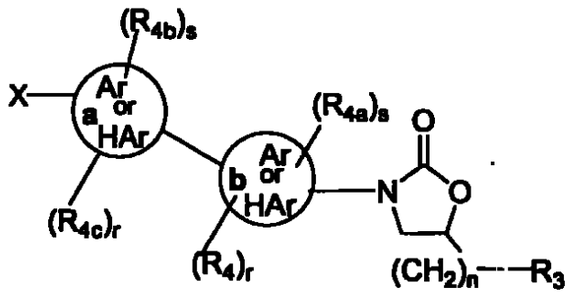
Background of the Invention

Oxazolidinones represent the first new class of antibacterials to be developed since the quinolones. The oxazolidinones are synthetic antibacterial compounds that are orally or intravenously active against problematic multidrug resistant Gram positive organisms and are not cross-resistant with other antibiotics. See Riedl et al, Recent Developments with Oxazolidinone Antibiotics, *Exp. Opin. Ther. Patents* (1999) 9(5), Ford et al., Oxazolidinones: New Antibacterial Agents, *Trends in Microbiology* 196 Vol.5, No. 5, May 1997 and WO 96/35691. See also WO 03/063862, WO 01/81350, WO 01/94342, WO 03/072553, EP 0352781 and US 5,565,571 and 4,053,593.

This invention relates to new oxazolidinones having a cyclopropyl moiety, which are effective against aerobic and anerobic pathogens such as multi-resistant staphylococc , streptococci and enterococci, Bacteroides spp., Clostridia spp. species, as well as acid-fast organisms such as *Mycobacterium tuberculosis* and other mycobacterial species.

Summary of the Invention

The present invention relates to compounds of formula I:



I

its enantiomer, diastereomer, or pharmaceutically acceptable salt, hydrate or prodrug thereof wherein:

R_1 represents

i) hydrogen,

ii) $(CH_2)_nNR_5R_6$,

iii) $CR_7R_8R_9$, $C(R)_2OR_{14}$, CH_2NHR_{14},

iv) $C(=O)R_{13}$, $C(=NOH)H$, $C(=NOR_{13})H$, $C(=NOR_{13})R_{13}$, $C(=NOH)R_{13}$, $C(=O)N(R_{13})_2$, $C(=NOH)N(R_{13})_2$, $NHC(=X_1)N(R_{13})_2$, $NRCO_2R$, $(C=NH)R_7$, $N(R_{13})C(=X_1)N(R_{13})_2$, $COOR_{13}$, SO_2R_{14}, $N(R_{13})SO_2R_{14}$, $N(R_{13})COR_{14}$,

v) $(C_{1-6}alkyl)CN$, CN, $CH=C(R)_2$, $(CH_2)_pOH$, $C(=O)CHR_{13}$, $C(=NR_{13})R_{13}$, $NR_{10}C(=X_1)R_{13}$; or

vi) C_{5-10} heterocycle optionally substituted with 1-3 groups of R_7, which may be attached through either a carbon or a heteroatom;

X represents 

; or a C_{5-10} heteroaryl represented by 

which represents an optionally substituted aromatic heterocyclic group containing 1to 4 nitrogen atoms and at least one double bond, and which is connected through a bond on any nitrogen said heteroaryl optionally substituted with 1 to 3 substitutents selected from R_7

Y represents NR^*, O, CN, or S(O)p;

represents aryl or heteroaryl, heterocycle, heterocyclyl or heterocyclic;

R_* represents hydrogen or C_{1-6} alkyl;

R_3 represent $NR(C=X_2)R_{12}$, NR^*R_{12}, C_{6-10} aryl, or $-(O)_nC_{5-10}$ heterocyclyl which may be attached through either a carbon or a heteroatom; said aryl and heterocyclyl optionally substituted with 1-3 groups of R_7,

R_4, R_{4a}, R_{4b}, and R_{4c} independently represent

i) hydrogen,

ii) halogen,

iii) C_{1-6} alkoxy, or

iv) C_{1-6} alkyl;

r and s independently are 1-3, with the provision that when $(R_{4a})_r$ and $(R_{4b})_r$ or (R_{4b}) and $(R_{4c})_s$ are attached to an Ar or HAr ring the sum of r and s is less than or equal to 4;

R_5 and R_6 independently represent

i) hydrogen,

ii) C_{1-6} alkyl optionally substituted with 1-3 groups of halogen, CN, OH, C_{1-6} alkoxy, amino, imino, hydroxyamino, alkoxyamino, C_{1-6} acyloxy, C_{1-6} alkylsulfenyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, aminosulfonyl, C_{1-6} alkylaminosulfonyl, C_{1-6} dialkylaminosulfonyl, 4-morpholinylsulfonyl, phenyl, pyridine, 5-isoxazolyl, ethylenyloxy, or ethynyl, said phenyl and pyridine optionally substituted with 1-3 halogen, CN, OH, CF_3, C_{1-6} alkyl or C_{1-6} alkoxy;

iii) C_{1-6} acyl optionally substituted with 1-3 groups of halogen, OH, SH, C_{1-6} alkoxy, naphthalenoxy, phenoxy, amino, C_{1-6} acylamino, hydroxylamino, alkoxylamino, C_{1-6} acyloxy, aralkyloxy, phenyl, pyridine, C_{1-6} alkylcarbonyl, C_{1-6} alkylamino, C_{1-6} dialkylamino, C_{1-6} hydroxyacyloxy, C_{1-6} alkylsulfenyl, phthalimido, maleimido, succinimido, said phenoxy, phenyl and pyridine optionally substituted with 1-3 groups of halo, OH, CN, C_{1-6} alkoxy, amino, C_{1-6} acylamino, CF_3 or C_{1-6} alkyl;

iv) C_{1-6} alkylsulfonyl optionally substituted with 1-3 groups of halogen, OH, C_{1-6} alkoxy, amino, hydroxylamino, alkoxylamino, C_{1-6} acyloxy, or phenyl; said phenyl optionally substituted with 1-3 groups of halo, OH, C_{1-6} alkoxy, amino, C_{1-6} acylamino, CF_3 or C_{1-6} alkyl;

v) arylsulfonyl optionally substituted with 1-3 of halogen, C_{1-6} alkoxy, OH or C_{1-6} alkyl;

vi) C_{1-6} alkoxycarbonyl optionally substituted with 1-3 of halogen, OH, C_{1-6} alkoxy, C_{1-6} acyloxy, or phenyl, said phenyl optionally substituted with 1-3 groups of halo, OH, C_{1-6} alkoxy, amino, C_{1-6} acylamino, CF_3 or C_{1-6} alkyl;

vii) aminocarbonyl, C_{1-6} alkylaminocarbonyl or C_{1-6} dialkylaminocarbonyl, said alkyl groups optionally substituted with 1-3 groups of halogen, OH, C_{1-6} alkoxy or phenyl

viii) five to six membered heterocycles optionally substituted with 1-3 groups of halogen, OH, CN, amino, C_{1-6} acylamino, C_{1-6} alkylsulfonylamino, C_{1-6} alkoxycarbonylamino, C_{1-6} alkoxy, C_{1-6} acyloxy or C_{1-6} alkyl, said alkyl optionally substituted with 1-3 groups of halogen, or C_{1-6} alkoxy;

ix) C_{3-6} cycloalkylcarbonyl optionally substituted with 1-3 groups of halogen, OH, C_{1-6} alkoxy or CN;

x) benzoyl optionally substituted with 1-3 groups of halogen, OH, C_{1-6} alkoxy, C_{1-6} alkyl, CF_3, C_{1-6} alkanoyl, amino or C_{1-6} acylamino;

xi) pyrrolylcarbonyl optionally substituted with 1-3 of C_{1-6} alkyl;

xii) C_{1-2} acyloxyacetyl where the acyl is optionally substituted with amino, C_{1-6} alkylamino, C_{1-6} dialkylamino, 4-morpholino, 4-aminophenyl, 4-(dialkylamino)phenyl, 4-(glycylamino)phenyl; or

R_5 and R_6 taken together with any intervening atoms can form a 3 to 7 membered heterocyclic ring containing carbon atoms and 1-2 heteroatoms independently chosen from O, S, SO, SO_2, N, or NR_8;

R_7 represent

i) hydrogen, halogen, $(CH2)_pC_{5-10}$ heterocyclyl, CN, CO_2R, $CON(R)_2$, CHO, $(CH_2)_{0-3}NHAc$, C(=NOR), OH, C_{1-6} alkoxy, C_{1-6} alkyl, alkenyl, hydroxy C_{1-6} alkyl, $(CH_2)_{1-3}NHC(O)C_{1-6}$ alkyl, $(CH_2)_{0-3}N(C_{1-6}$ alkyl$)_2$, $NHCO_2R$, $-OCOC_{1-6}$ alkyl;

ii) $(CH_2)_n$amino, $(CH_2)_nC1$-6 alkylamino, C_{1-6} acylamino, C_{1-6} dialkylamino, hydroxylamino or C_{1-2} alkoxyamino all of which can be optionally substituted on the nitrogen with C_{1-6} acyl, C_{1-6} alkylsulfonyl or C_{1-6} alkoxycarbonyl, said acyl and alkylsulfonyl optionally substituted with 1-2 of halogen or OH;

R_8 and R_9 independently represent

i) H, CN,

ii) C_{1-6} alkyl optionally substituted with 1-3 halogen, CN, OH, C_{1-6} alkoxy, C_{1-6} acyloxy, or amino,

iii) phenyl optionally substituted with 1-3 groups of halogen, OH, C_{1-6} alkoxy; or

R_7 and R_8 taken together can form a 3-7 membered carbon ring optionally interrupted with 1-2 heteroatoms chosen from O, S, SO, SO_2, NH, and NR_8;

X_1 represents O, S or NR_{13}, NCN, NCO_2R_{16}, or NSO_2R_{14}

X_2 represents O, S, NH or NSO_2R_{14};

R_{10} represents hydrogen, C_{1-6} alkyl or CO_2R_{15};

R_{12} represents hydrogen, C_{1-6} alkyl, NH_2, OR, CHF_2, $CHCl_2$, $C(R)_2Cl$, $(CH_2)_nSR$, $(CH_2)_nCN$, $(CH_2)_nSO_2R$, $(CH_2)_nS(O)R$, C_{1-6} alkylamino, C_{3-6} cycloalkyl, C_{5-10} heterocyclyl or C_{1-6} dialkylamino, where said alkyl, and cycloalkyl may be substituted with 1-3 groups of halo, CN, OH or C_{1-6} alkoxy, said heterocyclyl optionally substituted with 1-3 groups of R_7;

Each R_{13} represents independently hydrogen, C_{1-6} alkyl, C_{6-10} aryl, NR_5R_6, SR_8, $S(O)R_8$, $S(O)_2R_8$, CN, OH, C_{1-6} alkylS(O)R, C_{1-6} alkoxycarbonyl, hydroxycarbonyl, -OCOaryl, C_{1-6} acyl, C_{3-7} membered carbon ring optionally interrupted with 1-4 heteroatoms chosen from O, S, SO, SO_2, NH and NR_8 where said C_{1-6} alkyl, aryl or C_{1-6} acyl groups may be independently substituted with 0-3 halogens, hydroxy, $N(R)_2$, CO_2R, C_{6-10} aryl, C_{5-10} heteroaryl, or C_{1-6} alkoxy groups;
When two R_{13} groups are attached to the same atom or two adjacent atoms they may be taken together to form a 3-7 membered carbon ring optionally interrupted with 1-2 heteroatoms chosen from O, S, SO, SO_2, NH, and NR_8;

R represents hydrogen or C_{1-6} alkyl;

R* represents hydrogen, CN, $C(=O)R_{14}$, $(CH_2)_pCO_2C_{1-6}$ alkyl, $(CH_2)_pC_{5-10}$heterocyclyl, or C_{1-6} alkyl, said alkyl and heterocyclyl optionally substituted with 1 to 3 groups of R_7;

R_{14} represents amino, C_{1-6} alkyl, C_{3-6} cycloalkyl, $(CH_2)_pC_{5-10}$heterocyclyl, C_{1-6} haloalkyl, phenyl, said alkyl, cycloalkyl, phenyl, heterocyclyl optionally substituted with 1-3 group of R_7, when

R_7 is an amino or hydroxyl group or a nitrogen that forms part of the heterocycle, said amino and hydroxy optionally protected with an amino or hydroxy protecting group;

R_{15} is C_{1-6} alkyl or benzyl said benzyl optionally substituted with 1-3 groups of halo, OH, C_{1-6} alkoxy, amino, C_{1-6} acylamino, or C_{1-6} alkyl;

R_{16} is hydrogen, C_{5-10}heteroaryl, C_{6-10}aryl, said heteroaryl and aryl optionally substituted with 1-3 groups of R_7;

p represents 0-2 and

m, n and q independently represent 0-1.

Another aspect of the invention is concerned with the use of the novel antibiotic compositions in the treatment of bacterial infections.

Detailed Description of the Invention

The invention is described herein in detail using the terms defined below unless otherwise specified.

The compounds of the present invention may have asymmetric centers, chiral axes and chiral planes, and occur as racemates, racemic mixtures, and as individual diastereomers, with all possible isomers, including optical isomers, being included in the present invention. (See E.L. Eliel and S. H. Wilen Stereochemistry of Carbon Compounds (John Wiley and Sons, New York 1994, in particular pages 1119-1190).

When any variable (e.g. aryl, heterocycle, R_5, R_6 etc.) occurs more than once, its definition on each occurrence is independent at every other occurrence. Also combinations of substituents/or variables are permissible only if such combinations result in stable compounds.

The term "alkyl" refers to a monovalent alkane (hydrocarbon) derived radical containing from 1 to 15 carbon atoms unless otherwise defined. It may be straight or branched. Preferred alkyl groups include lower alkyls which have from 1 to 6 carbon atoms such as methyl, ethyl, propyl, isopropyl, butyl and t-butyl. When substituted, alkyl groups may be substituted with up to 3 substituent groups, selected from the groups as herein defined, at any available point of attachment. When the alkyl

group is said to be substituted with an alkyl group, this is used interchangeably with "branched alkyl group".

Cycloalkyl is a species of alkyl containing from 3 to 15 carbon atoms, without alternating or resonating double bonds between carbon atoms. It may contain from 1 to 4 rings which are fused. Preferred cycloalkyl groups are cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. When substituted, cycloalkyl groups may be substituted with up to 3 substituents which are defined herein by the definition of alkyl.

Alkanoyl refers to a group derived from an aliphatic carboxylic acid of 2 to 4 carbon atoms. Examples are acetyl, propionyl, butyryl and the like.

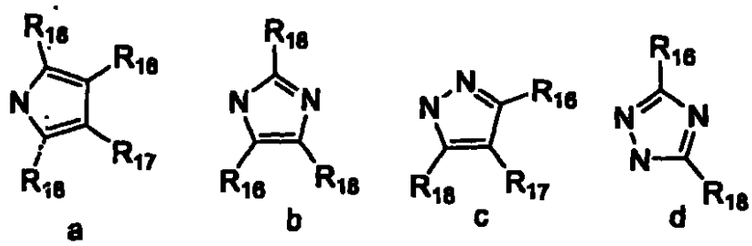
The term "alkoxy" refers to those groups of the designated length in either a straight or branched configuration and if two or more carbon atoms in length, they may include a double or a triple bond. Exemplary of such alkoxy groups are methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tertiary butoxy, pentoxy, isopentoxy, hexoxy, isohexoxy allyloxy, propargyloxy, and the like.

refers to aryl or heteroaryl, heterocycle, Het, heterocyclyl or heterocyclic as described immediately below.

Aryl refers to any stable monocyclic or bicyclic carbon ring of up to 7 atoms in each ring, wherein at least one ring is aromatic. Examples of such aryl elements include phenyl, napthyl, tetrahydronaphthyl, indanyl, indanonyl, biphenyl, tetralihyl, tetralonyl, fluorenonyl, phenanthryl, anthryl, acenaphthyl, and the like substituted phenyl and the like. Aryl groups may likewise be substituted as defined. Preferred substituted aryls include phenyl and naphthyl.

The term heterocycle, heteroaryl, Het, heterocyclyl or heterocyclic, as used herein except where noted, represents a stable 5- to 7-membered mono- or bicyclic or stable 8- to 11-membered bicyclic heterocyclic ring system, any ring of which may be saturated or unsaturated, and which consists of carbon atoms and from one to four heteroatoms selected from the group consisting of N, O and S, and wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized (in which case it is properly balanced by a counterion), and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom, which results in the creation of a stable structure. The term heterocycle or heterocyclic includes heteroaryl moieties.

"Heterocycle" or "heterocyclyl" therefore includes the above mentioned heteroaryls, as well as dihydro and tetrahydro analogs thereof. The heterocycle, heteroaryl, Het or heterocyclic may be substituted with 1-3 groups of R7. Examples of such heterocyclic elements include, but are not limited to the following: piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolodinyl, 2-oxoazepinyl, azepinyl, pyrrolyl, 4-piperidonyl, pyrrolidinyl, pyrazolyl, pyrazolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyridyl, pyrazinyl, pyrimidinyl, pyrimidonyl, pyridinonyl, pyridazinyl, oxazolyl, oxazolidinyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiazolyl, thiazolidinyl, isothiazolyl, quinuclidinyl, isothiazolidinyl, indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, thiadiazoyl, benzopyranyl, benzothiazolyl, benzoxazolyl, furyl, tetrahydrofuryl, tetrahydropyranyl, thiophenyl, imidazopyridinyl, triazolyl, tetrazolyl, triazinyl, thienyl, benzothienyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, naphthpyridinyl, dihydropyrimidinyl, dihydropyrrolyl, dihydroquinolinyl, dihydrotetrazolyl, dihydrotriazolyl, dihydrothienyl, dihydrooxazolyl, dihydrobenzothiophenyl, dihydrofuranyl, benzothiazolyl, benzothienyl, benzoimidazolyl, benzopyranyl, benzothiofuranyl, carbolinyl, chromanyl, cinnolinyl, benzopyrazolyl, benzodioxolyl and oxadiazolyl. Additional examples of heteroaryls are illustrated by formulas a, b, c and d:



wherein R_{16} and R_{17} are independently selected from hydrogen, halogen, C_{1-6} alkyl, C_{2-4} alkanoyl, C_{1-6} alkoxy; and R_{18} represents hydrogen, C_{1-6} alkyl, C_{2-4} alkanoyl, C_{1-6} alkoxycarbonyl and carbamoyl.

The term "alkenyl" refers to a hydrocarbon radical straight, branched or cyclic containing from 2 to 10 carbon atoms and at least one carbon to carbon double bond. Preferred alkenyl groups include ethenyl, propenyl, butenyl and cyclohexenyl.

The terms "quaternary nitrogen" and "positive charge" refer to tetravalent, positively charged nitrogen atoms (balanced as needed by a counterion known in the art) including, e.g., the positively charged nitrogen in a tetraalkylammonium group (e. g. tetramethylammonium), heteroarylium, (e.g., N-methyl-pyridinium), basic nitrogens which are protonated at physiological pH, and the like. Cationic groups thus encompass positively charged nitrogen-containing groups, as well as basic nitrogens which are protonated at physiologic pH.

The term "heteroatom" means O, S or N, selected on an independent basis.

The term "prodrug" refers to compounds which are drug precursors which, following administration and absorption, release the drug in vivo via some metabolic process. Exemplary prodrugs include acyl amides of the amino compounds of this inventon such as amides of alkanoic(C_{1-6})acids, amides of aryl acids (e.g., benzoic acid) and alkane(C_{1-6})dioic acids.

Halogen and "halo" refer to bromine, chlorine, fluorine and iodine.

When a group is termed "substituted", unless otherwise indicated, this means that the group contains from 1 to 3 substituents thereon.

When a functional group is termed "protected", this means that the group is in modified form to preclude undesired side reactions at the protected site. Suitable protecting groups for the compounds of the present invention will be recognized from the present application taking into account the level of skill in the art, and with reference to standard textbooks, such as Greene, T. W. et al. Protective Groups in Organic Synthesis Wiley, New York (1991). Examples of suitable protecting groups are contained throughout the specification.

Examples of suitable hydroxyl and amino protecting groups are: trimethylsilyl, triethylsilyl, o-nitrobenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, t-butyldiphenylsilyl, t-butyldimethylsilyl, benzyloxycarbonyl, t-butyloxycarbonyl, 2,2,2-trichloroethyloxycarbonyl, allyloxycarbonyl and the like. Examples of suitable carboxyl protecting groups are benzhydryl, o-nitrobenzyl, p-nitrobenzyl, 2-naphthylmethyl, allyl, 2-chloroallyl, benzyl, 2,2,2-trichloroethyl, trimethylsilyl, t-butyldimethylsilyl, t-butldiphenylsilyl, 2-(trimethylsilyl)ethyl, phenacyl, p-methoxybenzyl, acetonyl, p-methoxyphenyl, 4-pyridylmethyl, t-butyl and the like.

The cyclopropyl containing oxazolidinone compounds of the present invention are useful per se and in their pharmaceutically acceptable salt and ester forms for the treatment of bacterial infections in

animal and human subjects. The term "pharmaceutically acceptable ester, salt or hydrate," refers to those salts, esters and hydrated forms of the compounds of the present invention which would be apparent to the pharmaceutical chemist. i.e., those which are substantially non-toxic and which may favorably affect the pharmacokinetic properties of said compounds, such as palatability, absorption, distribution, metabolism and excretion. Other factors, more practical in nature, which are also important in the selection, are cost of the raw materials, ease of crystallization, yield, stability, solubility, hygroscopicity and flowability of the resulting bulk drug. Conveniently, pharmaceutical compositions may be prepared from the active ingredients in combination with pharmaceutically acceptable carriers. Thus, the present invention is also concerned with pharmaceutical compositions and methods of treating bacterial infections utilizing as an active ingredient the novel cyclopropyl containing oxazolidinone compounds.

The pharmaceutically acceptable salts referred to above also include acid addition salts. Thus, when the Formula I compounds are basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic or organic acids. Included among such acid salts are the following: acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, isethionic, lactate, maleate, mandelic, malic, maleic, methanesulfonate, mucic, 2-naphthalenesulfonate, nicotinate, nitric oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, phosphate, pantothenic, pamoic, sulfate, succinate, tartrate, thiocyanate, tosylate and undecanoate.

When the compound of the present invention is acidic, suitable "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium zinc and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium and sodium salts. Salts derived from pharmaceutically acceptable inorganic non-toxic bases include salts of primary, secondary and teritary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as arginine, betaine caffeine, choline, N,N^1-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine,

histidine, hydrabamine, isopropylamine, lysine, methylglucämine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine tripropylamine, tromethamine and the like.

The pharmaceutically acceptable esters are such as would be readily apparent to a medicinal chemist, and include those which are hydrolyzed under physiological conditions, such as "biolabile esters", pivaloyloxymethyl, acetoxymethyl, phthalidyl, indanyl and methoxymethyl, and others.

Biolabile esters are biologically hydrolizable, and may be suitable for oral administration, due to good absorption through the stomach or intenstinal mucosa, resistance to gastric acid degrada-tion and other factors. Examples of biolabile esters include compounds.

An embodiment of this invention is realized when R_1 independently represent H, NR_5R_6, CN, OH, or $CR_7R_8R_9$ and all other variables are as described herein.

Another embodiment of this invention is realized when 

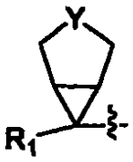
independently are phenyl, pyridyl, pyrimidinyl, or piperidinyl and all other variables are as described herein.

Another embodiment of this invention is realized when R_1 is CN and all other variables are as described herein.

An embodiment of this invention is realized when Y is NR* and all other variables are as described herein.

Another embodiment of this invention is realized when X is C_{5-10} heteroaryl represented by 

which represents an optionally substituted aromatic heterocyclic group containing 1to 4 nitrogen atoms and at least one double bond, and which is connected through a bond on any nitrogen. Exemplary groups are 1,2,3-triazole, 1,2,4-triazole, 1,2,5-triazole, tetrazole, pyrazole, and imidazole, any of which may contain 1 to 3 substitutents selected from R_7.

Another embodiment of this invention is realized when X is 

and all other variables are as described herein. A sub-embodiment of this invention is realized when Y is NR* and R_1 is CN or NH_2.

Another embodiment of this invention is realized when R_3 is C_{5-10} heteroaryl, said heteroaryl optionally substituted with 1-3 groups of R_7 and all other variables are as described herein.

Another embodiment of this invention is realized when R_3 is a C_{5-10} heteroaryl represented by 

which represents an optionally substituted aromatic heterocyclic group containing 1to 4 nitrogen atoms and at least one double bond, and which is connected through a bond on any nitrogen. Exemplary groups are 1,2,3-triazole, 1,2,4-triazole, 1,2,5-triazole, tetrazole, pyrazole, and imidazole, any of which may contain 1 to 3 substitutents selected from R_7.

Still another embodiment of this invention is realized when R_5 and R_6 independently are:

i) H,

ii) C_{1-6} alkyl optionally substituted with 1-3 groups of halogen, CN, OH, C_{1-6} alkoxy, amino, hydroxyamino, alkoxyamino, C_{1-6} acyloxy, C_{1-6} alkylsulfenyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyl, aminosulfonyl, C_{1-6} alkylaminosulfonyl, C_{1-6} dialkylaminosulfonyl, 4-morpholinylsulfonyl, phenyl, pyridine, 5-isoxazolyl, ethyenyloxy, or ethynyl, said phenyl and pyridine optionally substituted with 1-3 halogen, CN, OH, CF_3, C_{1-6} alkyl or C_{1-6} alkoxy;

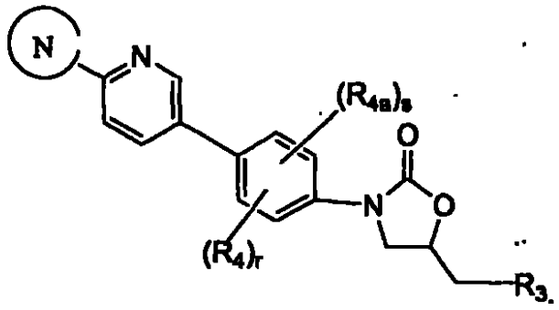
iii) C_{1-6} acyl optionally substituted with 1-3 groups of halogen, OH, SH, C_{1-6} alkoxy, naphthalenoxy, phenoxy, amino, C_{1-6} acylamino, hydroxylamino, alkoxylamino, C_{1-6} acyloxy, phenyl, pyridine, C_{1-6} alkylcarbonyl, C_{1-6} alkylamino, C_{1-6} dialkylamino, C_{1-6} hydroxyacyloxy, C_{1-6} alkylsulfenyl, phthalimido, maleimido, succinimido, said phenoxy,

phenyl and pyridine optionally substituted with 1-3 groups of halo, OH, CN, C_{1-6} alkoxy, amino, C_{1-6} acylamino, CF_3 or C_{1-6} alkyl; or

iv) benzoyl optionally substituted with 1-3 groups of halogen, OH, C_{1-6} alkoxy, C_{1-6} alkyl, CF3, C_{1-6} alkanoyl, amino or C_{1-6} acylamino and all other variables are as described herein.

Yet another embodiment of this invention is realized when X_1 represents O and all other variables are as described herein.

A preferred embodiment of this invention is realized when the structural formula is III:

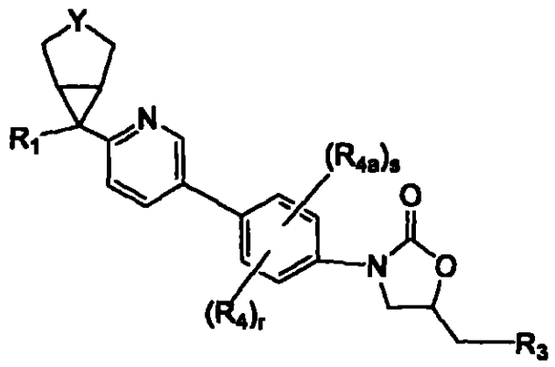


III

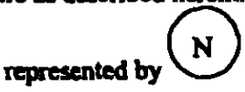
wherein R_4, R_{4a}, and R_3 are as described herein and  is 1,2,3-triazole, 1,2,4-triazole, 1,2,5-triazole, tetrazole, pyrazole, or imidazole, any of which may contain 1 to 3 substitutents selected from R_7.

A subembodiment of this invention is realized when R_3 is a C_{5-10} heteroaryl represented by  which represents an optionally substituted aromatic heterocyclic group containing 1 to 4 nitrogen atoms and at least one double bond, and which is connected through a bond on any nitrogen.

Another preferred embodiment of this invention is realized when the structural formula is IV:



Formula IV

wherein R_1, R_4, R_{4a}, Y and R_3 are as described herein. A subembodiment of this invention is realized when R3 is a C_{5-10} heteroaryl represented by  which represents an optionally substituted aromatic heterocyclic group containing 1 to 4 nitrogen atoms and at least one double bond, and which is connected through a bond on any nitrogen.

Preferred compounds of this invention are:

1-[5(R)-3-[4-[2-[(1α,5α,6β)-3-t-butoxycarbonyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]phenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]phenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole hydrochloride,

1-[5(R)-3-[4-[4-[(1α,5α,6β)-3-t-butoxycarbonyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]-3-fluorophenyl]phenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole,

1-[5(R)-3-[4-[4-[(1α,5α,6β)-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]-3-fluorophenyl]phenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole hydrochloride,

1-[5(R)-3-[4-[4-[(1α,5α,6β)-3-t-butoxycarbonyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]-3-fluorophenyl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole,

1-[5(R)-3-[4-[4-[(1α,5α,6β)-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]-3-fluorophenyl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole hydrochloride,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-3-t-butoxycarbonyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-yl]-1,2,3-triazole hydrochloride,

N-[5(S)-3-[4-[4-[(1α,5α,6β)-3-t-butoxycarbonyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]-3-fluorophenyl]phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide,
N-[5(S)-3-[4-[4-[(1α,5α,6β)-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]-3-fluorophenyl]phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide hydrochloride,
N-[5(S)-3-[4-[2-[(1α,5α,6β)-3-t-butoxycarbonyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide,
N-[5(S)-3-[4-[2-[(1α,5α,6β)-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide hydrochloride,
N-[5(S)-3-[4-[4-[(1α,5α,6β)-3-t-butoxycarbonyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]-3-fluorophenyl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]acetamide,
N-[5(S)-3-[4-[2-[(1α,5α,6β)-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]-3-fluorophenyl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]acetamide hydrochloride,
N-[5(S)-3-[4-[4-[(1α,5α,6β)-3-t-butoxycarbonyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]acetamide,
N-[5(S)-3-[4-[2-[(1α,5α,6β)-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]acetamide hydrochloride,
N-[5(S)-3-[4-[2-[(1α,5α,6β)-6-t-butoxycarbonylamino-3-oxabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]acetamide,
N-[5(S)-3-[4-[2-[(1α,5α,6β)-6-amino-3-oxabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]acetamide,
1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-t-butoxycarbonylamino-3-oxabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole,
1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-amino-3-oxabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole,
N-[5(S)-3-[4-[4-[(1α,5α,6β)-6-cyano-3-oxabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]acetamide,
1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-cyano-3-oxabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole,
N-[5(S)-3-[4-[2-[(1α,5α,6β)-6-t-butoxycarbonylamino-3-oxabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide,
N-[5(S)-3-[4-[2-[(1α,5α,6β)-6-amino-3-oxabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide,

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1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-t-butoxycarbonylamino-3-oxabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]phenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole,
1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-amino-3-oxabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]phenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole,
N-[5(S)-3-[4-[4-[(1α,5α,6β)-6-cyano-3-oxabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]phenyl]-2-oxooxazolidin-5-ylmethyl]acetamide,
1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-cyano-3-oxabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]phenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole,
1-[5(R)-3-[3-Fluoro-4-[2-(1-methyltetrazol-5-yl)pyridin-5-yl]phenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole,
1-[5(R)-3-[3,5-Difluoro-4-[2-(1-methyltetrazol-5-yl)pyridin-5-yl]phenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole,
1-[5(R)-3-[4-[4-[(1α,5α,6β)-3-t-butoxycarbonyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]-3,5-difluorophenyl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole,
1-[5(R)-3-[4-[4-[(1α,5α,6β)-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]-3,5-difluorophenyl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole,
N-[5(S)-3-[4-[4-[(1α,5α,6β)-3-t-butoxycarbonyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3,5-difluorophenyl]-2-oxooxazolidin-5-ylmethyl]acetamide,
N-[5(S)-3-[4-[4-[(1α,5α,6β)-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3,5-difluorophenyl]-2-oxooxazolidin-5-ylmethyl]acetamide hydrochloride,
N-[5(S)-3-[4-[4-[(1α,5α,6β)-3-t-butoxycarbonyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]-3,5-difluorophenyl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]acetamide,
N-[5(S)-3-[4-[4-[(1α,5α,6β)-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]-3,5-difluorophenyl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]acetamide hydrochloride,
N-[5(S)-3-[4-[4-[(1α,5α,6β)-3-t-butoxycarbonyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]phenyl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]acetamide,
N-[5(S)-3-[4-[4-[(1α,5α,6β)-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]phenyl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]acetamide,
N-[5(S)-3-[4-[4-[(1α,5α,6β)-3-t-butoxycarbonyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]-3-fluorophenyl]-3,5-difluorophenyl]-2-oxooxazolidin-5-ylmethyl]acetamide,

N-[5(S)-3-[4-[4-[(1α,5α,6β)-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]-3-fluorophenyl]-3,5-difluorophenyl]-2-oxooxazolidin-5-ylmethyl]acetamide,

1-[5(R)-3-[4-[4-[(1α,5α,6β)-3-t-butoxycarbonyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]-3-fluorophenyl]-3,5-difluorophenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole,

1-[5(R)-3-[4-[4-[(1α,5α,6β)-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]-3-fluorophenyl]-3,5-difluorophenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole hydrochloride,

1-[5(R)-3-[4-[4-[(1α,5α,6β)-3-t-butoxycarbonyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3,5-difluorophenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole,

1-[5(R)-3-[4-[4-[(1α,5α,6β)-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3,5-difluorophenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole

1-[5(R)-3-[4-[4-[(1α,5α,6β)-3-t-butoxycarbonyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]phenyl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole,

1-[5(R)-3-[4-[4-[(1α,5α,6β)-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]phenyl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-t-butoxycarbonylamino-3-oxabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3,5-difluorophenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-amino-3-oxabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3,5-difluorophenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole,

N-[5(S)-3-[4-[2-[(1α,5α,6β)-6-t-butoxycarbonylamino-3-oxabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3,5-difluorophenyl]-2-oxooxazolidin-5-ylmethyl]acetamide,

N-[5(S)-3-[4-[2-[(1α,5α,6β)-6-amino-3-oxabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3,5-difluorophenyl]-2-oxooxazolidin-5-ylmethyl]acetamide,

N-[5(S)-3-[4-[2-[(1α,5α,6β)-6-cyano-3-oxabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3,5-difluorophenyl]-2-oxooxazolidin-5-ylmethyl]acetamide,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-cyano-3-oxabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3,5-difluorophenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole,

N-[5(S)-3-[4-[2-[(1α,5α,6β)-6-cyano-3-thiabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]acetamide,

N-[5(S)-3-[4-[2-[(1α,5α,6β)-6-cyano-3-thiabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]acetamide S-oxide,

N-[5(S)-3-[4-[2-[(1α,5α,6β)-6-cyano-3-thiabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]acetamide S,S-dioxide,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-cyano-3-thiabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-cyano-3-thiabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole S-oxide,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-cyano-3-thiabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole S,S-dioxide,

4-[5(R)-3-[4-[2-[(1α,5α,6β)-3-t-butoxycarbonyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,4-triazole,

4-[5(R)-3-[4-[2-[(1α,5α,6β)-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,4-triazole,

5(R)-3-[4-[2-[(1α,5α,6β)-3-t-butoxycarbonyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-5-[(isoxazol-3-yl)oxy]methyloxazolidin-2-one,

5(R)-3-[4-[2-[(1α,5α,6β)-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-5-[(isoxazol-3-yl)oxy]methyloxazolidin-2-one,

5(R)-3-[4-[2-[(1α,5α,6β)-3-t-butoxycarbonyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-5-[N-(t-butoxycarbonyl)-N-(isoxazol-3-yl)]aminomethyloxazolidin-2-one,

5(R)-3-[4-[2-[(1α,5α,6β)-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-5-[N-(isoxazol-3-yl)]aminomethyloxazolidin-2-one,

5(R)-3-[4-[2-[(1α,5α,6β)-6-cyano-3-oxabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-5-[(isoxazol-3-yl)oxy]methyloxazolidin-2-one,

5(R)-5-[N-(t-butoxycarbonyl)-N-(isoxazol-3-yl)]aminomethyl-3-[4-[2-[(1α,5α,6β)-6-cyano-3-oxabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]oxazolidin-2-one,

5(R)-3-[4-[2-[(1α,5α,6β)-6-cyano-3-oxabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-5-[N-(isoxazol-3-yl)]aminomethyloxazolidin-2-one,

N-[5(S)-3-[4-[2-[(1α,5α,6β)-6-cyano-3-oxabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]propionamide,

N-[5(S)-3-[4-[2-[(1α,5α,6β)-6-cyano-3-oxabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]difluoroacetamide,

N-[5(S)-3-[4-[2-[(1α,5α,6β)-6-cyano-3-oxabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]cyclopropanecarboxamide,

N-[5(S)-3-[4-[2-[(1α,5α,6β)-3-t-butoxycarbonyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]propionamide,

N-[5(S)-3-[4-[2-[(1α,5α,6β)-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]propionamide,

N-[5(S)-3-[4-[2-[(1α,5α,6β)-3-t-butoxycarbonyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]cyclopropanecarboxamide,

N-[5(S)-3-[4-[2-[(1α,5α,6β)-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]cyclopropanecarboxamide,

N-[5(S)-3-[4-[2-[(1α,5α,6β)-3-t-butoxycarbonyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]difluoroacetamide,

N-[5(S)-3-[4-[2-[(1α,5α,6β)-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]difluoroacetamide,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-cyano-3-methyl-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-3,6-dicyano-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-3-[(1-t-butoxycarbonylaminocyclopropan-1-yl)carbonyl]-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-3-[(1-aminocyclopropan-1-yl)carbonyl]-6-cyano-3-azabicyclo [3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-cyano-3-[2-(phthalimid-2-yl)ethyl]-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-3-(2-aminoethyl)-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-cyano-3-[2-(1,2,4-triazol-4-yl)ethyl]-3-azabicyclo[3.1.0] hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-3-bromoacetyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-cyano-3-(morpholin-4-yl)acetyl-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-cyano-3-(5-cyanopyridin-2-yl)-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-cyano-3-(1,3-dihydroxypropan-2-yl)-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-3-[((2S)-1-t-butoxycabonylpyrrolidin-2-yl)carbonyl]-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-cyano-3-[((2S)-pyrrolidin-2-yl)carbonyl]-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-3-[((2S,4R)-1-t-butoxycabonyl-4-hydroxypyrrolidin-2-yl)carbonyl]-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole,1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-cyano-3-[((2S,4R)-4-hydroxypyrrolidin-2-yl)carbonyl]-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-3-[((2S,4S)-1-t-butoxycabonyl-4-fluoropyrrolidin-2-yl)carbonyl]-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-cyano-3-[((2S,4S)-4-fluoropyrrolidin-2-yl)carbonyl]-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole,

1-[5(R)-3-[4-[4-[(1α,5α,6β)-3-t-butoxycarbonyl-6-(t-butoxycarbonyl)amino-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole,

1-[5(R)-3-[4-[4-[(1α,5α,6β)-6-amino-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole dihydrochloride,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-3-acetoxyacetyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-cyano-3-hydroxyacetyl-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole,

N-[5(S)-3-[4-[2-[(1α,5α,6β)-3-t-butoxycarbonyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]-(2,2-dichlorocyclopropane)-1-carboxamide,

N-[5(S)-3-[4-[2-[(1α,5α,6β)-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]-(2,2-dichlorocyclopropane)-1-carboxamide,

N-[5(S)-3-[4-[2-[(1α,5α,6β)-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]-(2,2-dichlorocyclopropane)-1-carboxamide,

N-[5(S)-3-[4-[2-[(1α,5α,6β)-3-t-butoxycarbonyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]-(2,2-difluorocyclopropane)-1-carboxamide,

N-[5(S)-3-[4-[2-[(1α,5α,6β)-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]-(2,2-difluorocyclopropane)-1-carboxamide,

N-[5(S)-3-[4-[2-[(1α,5α,6β)-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]-(2,2-difluorocyclopropane)-1-carboxamide,

O-methyl-N-[5(S)-3-[4-[2-[(1α,5α,6β)-3-t-butoxycarbonyl-6-cyano-3-azabicyclo[3.1.0] hexan-6-yl]- pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]carbamate,

O-methyl-N-[5(S)-3-[4-[2-[(1α,5α,6β)-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]carbamate,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-3,6-dicyano-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3,5-difluorophenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-cyano-3-methyl-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3,5-difluorophenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole,

1-[5(R)-3-[3-fluoro-4-[2-[(1α,5α,6β)-6-hydroxymethyl-3-oxabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]phenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-cyano-3-oxabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]-4-fluoro-1,2,3-triazole,

1-[5(R)-3-[4-[4-[(1α,5α,6β)-3-t-butoxycarbonyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]-4-fluoro-1,2,3-triazole,

1-[5(R)-3-[4-[4-[(1α,5α,6β)-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]-4-fluoro-1,2,3-triazole,

1-[5(R)-3-[4-[4-[(1α,5α,6β)-3-t-butoxycarbonyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]-5-fluoro-1,2,3-triazole,

1-[5(R)-3-[4-[4-[(1α,5α,6β)-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]-5-fluoro-1,2,3-triazole,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-3-(4-t-butoxycarbonylpiperazin-1-yl)acetyl-6-cyano-3-azabicyclo [3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-cyano-3-(piperazin-1-yl)acetyl-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole dihydrochloride,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-cyano-3-oxabicyclo[3.1.0]hexan-6-yl]thiophen-4-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-cyano-3-(piperidin-1-yl)acetyl-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-cyano-3-(pyrrolidin-1-yl)acetyl-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-cyano-3-(4-dimethylaminopiperidin-1-yl)acetyl-3-azabicyclo [3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-3-[((2S)-1-t-butoxycabonylpyrrolidin-2-yl)carbonyl]-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3,5-difluorophenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-cyano-3-[((2S)-pyrrolidin-2-yl)carbonyl]-3-azabicyclo[3.1.0] hexan-6-yl]pyridin-5-yl]-3,5-difluorophenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-cyano-3-[((2S,4R)-4-hydroxypyrrolidin-2-yl)carbonyl]-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3,5-difluorophenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole hydrochloride,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-3-[((2S,4R)-1-t-butoxycabonyl-4-hydroxypyrrolidin-2-yl)carbonyl]-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3,5-difluorophenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-3-[((2S,4S)-1-t-butoxycabonyl-4-fluoropyrrolidin-2-yl)carbonyl]-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3,5-difluorophenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-cyano-3-[((2S,4S)-4-fluoropyrrolidin-2-yl)carbonyl]-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3,5-difluorophenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-t-butoxycarbonylamino-3-thiabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-amino-3-thiabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-t-butoxycarbonylamino-3-thiabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole S-oxide,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-amino-3-thiabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole S-oxide,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-t-butoxycarbonylamino-3-thiabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole S,S-dioxide,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-amino-3-thiabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole S,S-dioxide,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-t-butoxycarbonylamino-3-thiabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3,5-difluorophenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-amino-3-thiabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3,5-difluorophenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-t-butoxycarbonylamino-3-thiabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3,5-difluorophenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole S-oxide,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-amino-3-thiabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3,5-difluorophenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole S-oxide,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-t-butoxycarbonylamino-3-thiabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3,5-difluorophenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole S,S-dioxide,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-amino-3-thiabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3,5-difluorophenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole S,S-dioxide,

5(R)-3-[4-[2-[(1α,5α,6β)-3-t-butoxycarbonyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3,5-difluorophenyl]-5-[(isoxazol-3-yl)oxy]methyloxazolidin-2-one,

5(R)-3-[4-[2-[(1α,5α,6β)-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3,5-difluorophenyl]-5-[(isoxazol-3-yl)oxy]methyloxazolidin-2-one,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-cyano-3-(4-methylpiperazin-1-yl)acetyl-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-cyano-3-thiabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]phenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-cyano-3-thiabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]phenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole S-oxide,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-cyano-3-thiabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]phenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole S,S-dioxide,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-cyano-3-thiabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3,5-difluorophenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-cyano-3-thiabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3,5-difluorophenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole S-oxide,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-cyano-3-thiabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3,5-difluorophenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole S,S-dioxide,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-cyano-3-(1,3-diacetoxypropan-2-yl)-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-3-[(3R,4S)-1-azabicyclo[2.2.1]hepan-3-yl]carbonyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-cyano-3-(pyridin-2-yl)-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole,

5(R)-3-[4-[2-[(1α,5α,6β)-3-t-butoxycarbonyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3,5-difluorophenyl]-5-[N-(t-butoxycarbonyl)-N-(isoxazol-3-yl)]aminomethyloxazolidin-2-one,

5(R)-3-[4-[2-[(1α,5α,6β)-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3,5-difluorophenyl]-5-[N-(isoxazol-3-yl)]aminomethyloxazolidin-2-one,

1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-cyano-3-(thiatriazol-2-yl)-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole,

N-[5(S)-3-[4-[2-[(1α,5α,6β)-3-t-butoxycarbonyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]thioacetamide,

N-[5(S)-3-[4-[2-[(1α,5α,6β)-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]thioacetamide,

N-[5(S)-3-[4-[2-[(1α,5α,6β)-3-t-butoxycarbonyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]isothiocyanate,

O-methyl-N-[5(S)-3-[4-[2-[(1α,5α,6β)-3-t-butoxycarbonyl-6-cyano-3-azabicyclo[3.1.0] hexan-6-yl]- pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl] thiocarbamate,

O-methyl-N-[5(S)-3-[4-[2-[(1α,5α,6β)-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]thiocarbamate,

or their enantiomer, diastereomer, or pharmaceutically acceptable salt, hydrate or prodrug thereof.

Suitable subjects for the administration of the formulation of the present invention include mammals, primates, man, and other animals. *In vitro* antibacterial activity is predictive of *in vivo* activity when the compositions are administered to a mammal infected with a susceptible bacterial organism.

Using standard susceptibility tests, the compositions of the invention are determined to be active against MRSA and enterococcal infections.

The compounds of the invention are formulated in pharmaceutical compositions by combining the compounds with a pharmaceutically acceptable carrier. Examples of such carriers are set forth below. The compounds may be employed in powder or crystalline form, in liquid solution, or in suspension. They may be administered by a variety of means; those of principal interest include: topically, orally and parenterally by injection (intravenously or intramuscularly).

Compositions for injection, a preferred route of delivery, may be prepared in unit dosage form in ampules, or in multidose containers. The injectable compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain various formulating agents. Alternatively, the active ingredient may be in powder (lyophilized or non-lyophilized) form for reconstitution at the time of delivery with a suitable vehicle, such as sterile water. In injectable compositions, the carrier is typically comprised of sterile water, saline or another injectable liquid, e.g., peanut oil for intramuscular injections. Also, various buffering agents, preservatives and the like can be included.

Topical applications may be formulated in carriers such as hydrophobic or hydrophilic bases to form ointments, creams, lotions, in aqueous, oleaginous or alcoholic liquids to form paints or in dry diluents to form powders.

Oral compositions may take such forms as tablets, capsules, oral suspensions and oral solutions. The oral compositions may utilize carriers such as conventional formulating agents, and may include sustained release properties as well as rapid delivery forms.

The dosage to be administered depends to a large extent upon the condition and size of the subject being treated, the route and frequency of administration, the sensitivity of the pathogen to the particular compound selected, the virulence of the infection and other factors. Such matters, however, are left to the routine discretion of the physician according to principles of treatment well known in the antibacterial arts. Another factor influencing the precise dosage regimen, apart from the nature of the infection and peculiar identity of the individual being treated, is the molecular weight of the compound.

The novel antibiotic compositions of this invention for human delivery per unit dosage, whether liquid or solid, comprise from about 0.01% to as high as about 99% of the cyclopropyl containing oxazolidinone compounds discussed herein, the preferred range being from about 10-60% and from about 1% to about 99.99% of one or more of other antibiotics such as those discussed herein, preferably from about 40% to about 90%. The composition will generally contain from about 125 mg to about 3.0 g of the cyclopropyl containing oxazolidinone compounds discussed herein; however, in general, it is preferable to employ dosage amounts in the range of from about 250 mg to 1000 mg and from about 200mg to about 5 g of the other antibiotics discussed herein; preferably from about 250 mg to about 1000 mg. In parenteral administration, the unit dosage will typically include the pure compound in sterile water solution or in the form of a soluble powder intended for solution, which can be adjusted to neutral pH and isotonic.

The invention described herein also includes a method of treating a bacterial infection in a mammal in need of such treatment comprising administering to said mammal the claimed composition in an amount effective to treat said infection.

Oxazolidinones have been known at times to cause side effects such as sideroblastic anemia, peripheral sensory neuropathy, optic neuropathy, seizures, thrombocytopenia, cheilosis, seborrheic dermatitis, hypo-regenerative anemia, megaloblastic anemia or normocytic anemia. The compounds of the invention may be combined with an effective amount of one or more vitamins to prevent or reduce the occurrence of oxazolidinone-associated side effects in patients. The vitamins that can be combined are vitamin B2, vitamin B6, vitaimin B12 and folic acid. The vitamins may be administered with the oxazolidinones as separate compositions or the vitamins and oxazolidinones may be present in the same composition.

Thus another aspect of this invention is a method of treating or preventing an oxazolidinone-associated side effect by administering an effective amount of the oxazolidinone of structural formula I and an effective amount of one or more of vitamin B2, vitamin B6, vitaimin B12 and folic acid to a patient in need thereof.

A further aspect of this invention relates to a method of treating or preventing oxazolidinone-associated normocyctic anemia or peripheral sensory neuropathy by administering an effective amount of vitamin B2 to a patient in need thereof.

Yet another aspect of this invention relates to a method of treating or preventing oxazolidinone-associated sideroblastic anemia, peripheral sensory neuropathy, optic neuropathy, seizures,

thrombocytopenia, cheilosis, and seborrheic dermatitis by administering an effective amount of vitamin B6 to a patient in need thereof.

Still another aspect of this invention relates to a method of treating or preventing oxazolidinone-associated hypo-regenerative anemia, megaloblastic anemia by administering an effective amount of vitamin B12 and folic acid to a patient in need thereof.

Still another aspect of this invention relates to a method of treating or preventing bacterial infection by administering an effective amount of a compound of formula I and an effective amount of one or more of the group selected from the group consisting of vitamin B2, vitamin B6, vitaimin B12 and folic acid to a patient in need thereof.

The preferred methods of administration of the claimed compositions include oral and parenteral, e.g., i.v. infusion, i.v. bolus and i.m. injection formulated so that a unit dosage comprises a therapeutically effective amount of each active component or some submultiple thereof.

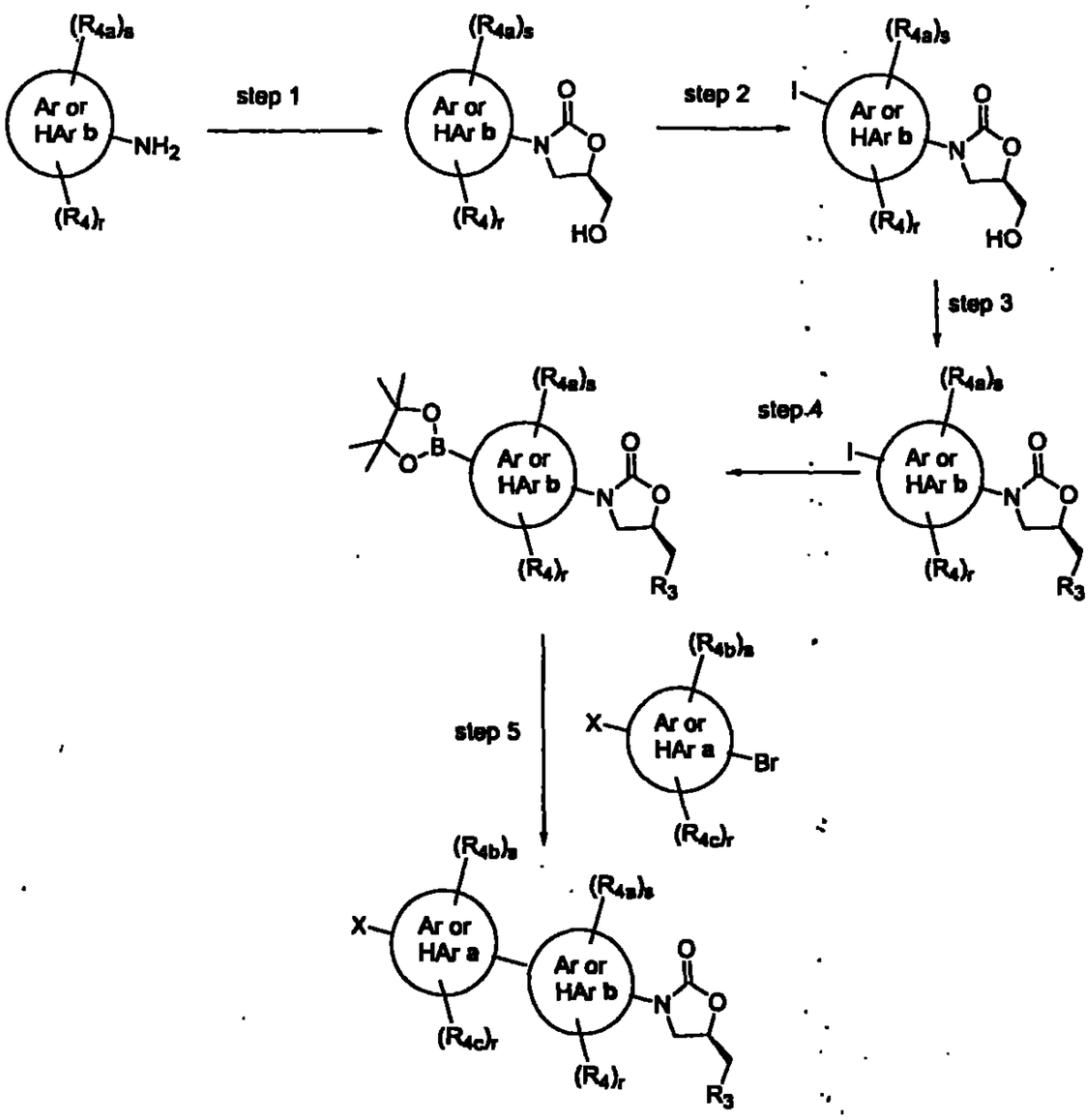
For adults, about 5-50 mg/kg of body weight, preferably about 250 mg to about 1000 mg per person of the cyclopropyl containing oxazolidinone antibacterial compound and about 250 mg, to about 1000 mg per person of the other antibiotic(s) given one to four times daily is preferred. More specifically, for mild infections a dose of about 250 mg two or three times daily of the cyclopropyl containing oxazolidinone antibacterial compound and about 250 mg two or three times daily of the other antibiotic is recommended. For moderate infections against highly susceptible gram positive organisms a dose of about 500 mg each of the cyclopropyl containing oxazolidinone and the other antibiotics, three or four times daily is recommended. For severe, life-threatening infections against organisms at the upper limits of sensitivity to the antibiotic, a dose of about 500-2000 mg each of the cyclopropyl-containing oxazolidinone compound and the other antibiotics, three to four times daily may be recommended.

For children, a dose of about 5-25 mg/kg of body weight given 2, 3, or 4 times per day is preferred; a dose of 10 mg/kg is typically recommended.

The compounds of the present invention can be prepared according to the procedures of the following scheme and general examples, using appropriate materials, and are further exemplified by the following specific examples. The compounds illustrated in the examples are not, however, to be construed as forming the only genus that is considered as the invention. The following examples further illustrate details for the preparation of compounds of the present invention. Those skilled in the art will readily understand that known variations of the conditions and processes of the following

preparative procedures can be used to prepare the compounds of the present invention. All temperatures are in degrees Celsius unless otherwise noted.

Scheme I



The compounds of the present invention can be prepared according to Scheme I, using appropriate materials, and are further exemplified by the following specific examples. The compounds illustrated in the examples are not, however, to be construed as forming the only genus

that is considered as the invention. The following examples further illustrate details for the preparation of compounds of the present invention. Those skilled in the art will readily understand that known variations of the conditions and processes of the following preparative procedures can be used to prepare the compounds of the present invention. All temperatures are in degrees Celsius unless otherwise noted.

In step 1 aromatic or heteroaromatic amines are converted to the corresponding 5-hydroxyoxazolidinones by methods well known to those skilled in the art. Typical conditions include acylation of the amine with a benzyloxycarbonyl chloride to afford the corresponding carbamate which is then deprotonated with a suitable strong base such n-butyl lithium, lithium t-butoxide or the like and the resulting anion quenched with the requisite glycidylbutyrate or other suitable glycidyl ester. Upon workup and purification the hydroxymethyloxazolidinone is obtained. It will be recognized to one skilled in the art that the requisite acylation may be catalyzed at the discretion of the experimenter by a number of suitable organic or inorganic bases and that likewise a number of suitable acylating agents can be envisaged for the performance of step 1. Moreover it should also be noted that if step 1 is performed using an R-glycidyl ester then the resulting 5-hydroxymethyl oxazolidinone will the S-configuration while performance of step 1 with an S-glycidyl ester will result in a 5-hydroxymethyl oxazolidinone with the R-configuration.

In step 2 the aromatic ring is halogenated using a suitable electrophilic halogenating agent undaer appropriate conditions. An example of such a halogenationg agent is iodine monochloride, but one skilled in the art will be quick to recognize that other halogenating agents could be used. One will recognize that if the desired halogen is an iodide, then an iodinating agent will be used but if another halogen is desired, then an appropriate halogenating agent will need to be chosen. These are well known to those of only ordinary skill in the art.

Step 3 describes the modification of the hydroxyl group to the R_3 substituent as described in the specification. It will be recognized that the exact procedures, conditions, and reagents will vary depending on the precise chemical nature of the R_3 substituent desired and representative transformations are described, but not limited to, those in the specific examples.

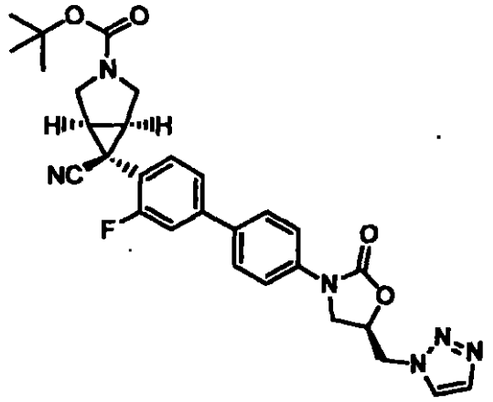
Step 4 describes the conversion of the aromatic halogen to a suitable boronate or boronic acid which is a suitable precursor for the subsequent coupling to AR or HAr a. These conditions are well known to one skilled in the art and include treatment of the starting halide with bispinacolato diboron or another suitable boron precursor in the presence of an appropriate Pd(II) catalyst such as [bis-

(diphenylphosphino)ferrocene] palladium II dichloride methylene chloride complex or the like and a suitable base.

Step 5 describes the coupling of the HAr(or AR)b component with a suitable HAr(or AR)a component as detailed in the specification . This transformation, commonly referred to a Suzuki coupling by this skilled in the art is catalyzed by a palladium (0) species such as tetrakis(triphenylphosphine)palladium (0) in the presence ao a suitable base such as alkali metal carbonate to give the compounds iof the present invention. Subsequent chemical transformations, well known to those skilled in the art, can be used to interconvert various members of the broad genus described and delineated as X in the specification.

The invention is further described in connection with the following non-limiting examples.

EXAMPLE 1



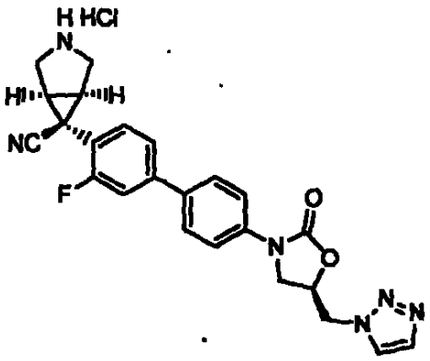
1-[5(R)-3-[4-[4-[(1α,5α,6β)-3-t-Butoxycarbonyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]-3-fluorophenyl]phenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole.

The mixture of 1-[5(R)-3-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolyl)phenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole (20.0 mg), 1-bromo-4-[(1α,5α,6β)-3-t-butoxycarbonyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]-3-fluorobenzene (19.7 mg) and tetrakis(tripheny'phosphine)palladium (0) (6.2 mg) in dioxane (0.5 mL) and 2M sodium carbonate solution (135 µL) was heated at 80 °C for 4 hours. The mixture was diluted with ethyl acetate and washed with saturated sodium hydrogencarbonate solution. The organic extracts were washed with brine, dried over anhydrous magnesium sulfate, and then concentrated in vacuo. Preparative thin-layer chromatography (silica, ethyl acetate: acetone = 9:1) of the residue gave title compound 1 (19.4 mg)

MS (FAB^+) *m/z*: 545 (MH^+).

HRMS (FAB$^+$) for $C_{29}H_{30}FN_6O_4$ (MH^+): calcd, 545.2313; found, 545.2341.

EXAMPLE 2



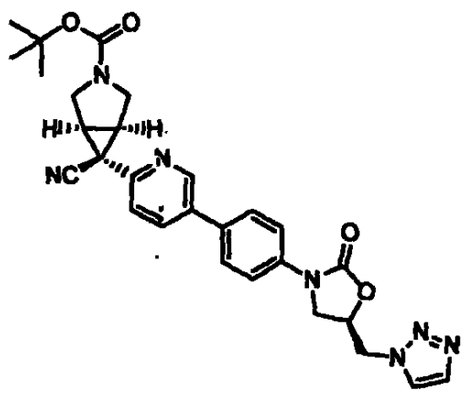
1-[5(R)-3-[4-[4-[(1α,5α,6β)-6-Cyano-3-azabicyclo[3.1.0]hexan-6-yl]-3-fluorophenyl]phenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole Hydrochloride.

To a solution of 1-[5(R)-3-[4-[4-[(1α,5α,6β)-3-t-butoxycarbonyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]-3-fluorophenyl]phenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole (316 mg) in dichloromethane-methanol (10:1) solution (2.5 mL) was added a solution of hydrogen chloride in dioxane (4M, 2.5 mL) was stirred at room temperature for 3.5 hours, then concentrated in vacuo. Treatment with ethanol of the residue gave title compound 2 (236 mg).

MS (FAB$^+$) *m/z*: 445 (MH^+) (as free base).

HRMS (FAB$^+$) for $C_{24}H_{22}FN_6O_2$ (MH^+): calcd, 445.1788; found, 445.1765.

EXAMPLE 3



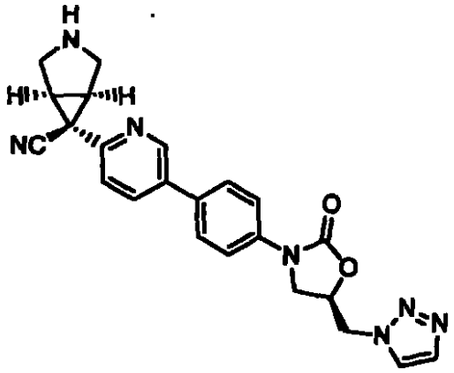
1-[5(R)-3-[4-[2-[(1α,5α,6β)-3-t-Butoxycarbonyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]phenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole.

Title compound 3 (22.3 mg) was prepared from 1-[5(R)-3-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolyl)phenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole (20.0 mg) and 5-bromo-2-[(1α,5α,6β)-3-t-butoxycarbonyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]pyridine (19.7 mg) in the same manner as described for EXAMPLE 1.

MS (FAB^+) *m/z*: 528 (MH^+).

HRMS (FAB^+) for $C_{29}H_{30}N_7O_4$ (MH^+): calcd, 528.2359; found, 528.2352.

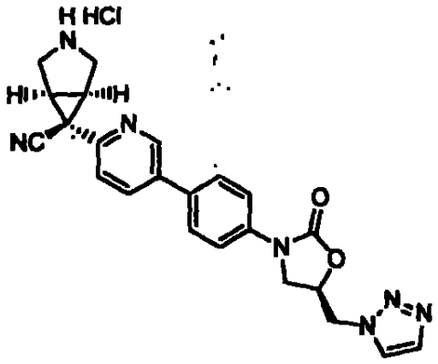
EXAMPLE 4



1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-Cyano-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]phenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole.

To a solution of 1-[5(R)-3-[4-[2-[(1α,5α,6β)-3-t-butoxycarbonyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]phenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole (209 mg) in dichloromethane-methanol (10:1) solution (1.7 mL) was added a solution of hydrogen chloride in dioxane (4M, 1.7 mL), the mixture was stirred at room temperature for 2.5 hours, then concentrated in vacuo. After dilution of the residue with dichloromethane-methanol (10:1) solution, the mixture was made to alkaline by the addition of 2 N sodium hydroxide solution. The resulting mixture was extracted with dichloromethane-methanol (10:1) solution. The organic extracts were dried over anhydrous magnesium sulfate, and then concentrated in vacuo. Flash chromatography (silica, dichloromethane: methanol = 10:1) of the residue gave title compound 5 (134 mg).

EXAMPLE 5



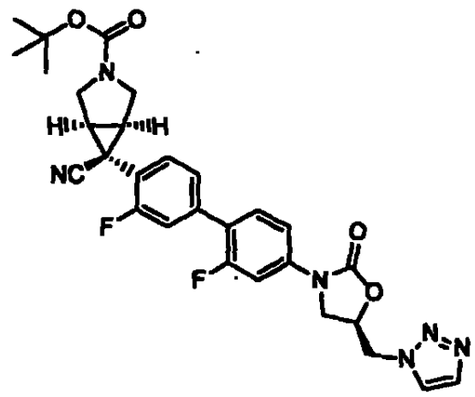
1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-Cyano-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]phenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole Hydrochloride.

To a solution of 1-[5(R)-3-[4-[2-[(1α,5α,6β)-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]pyridin-5-yl]phenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole (287 mg) in dichloromethane-methanol (10:1) solution (2.5 mL) was added a solution of hydrogen chloride in dioxane (4M, 168 μL) at 0 °C, the mixture was concentrated in vacuo. Treatment of the residue with ethanol gave title compound 5 (292 mg).

MS (EI^+) *m/z*: 428 (M^+) (as free base).

HRMS (EI^+) for $C_{23}H_{23}N_7O_3$ (M^+): calcd, 428.1835; found, 428.1848.

EXAMPLE 6



1-[5(R)-3-[4-[4-[(1α,5α,6β)-3-t-Butoxycarbonyl-6-cyano-3-azabicyclo[3.1.0]hexan-6-yl]-3-fluorophenyl]-3-fluorophenyl]-2-oxooxazolidin-5-ylmethyl]-1,2,3-triazole.