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ESCOBAR - URIBE ASOCIADOS

A B O G A D O S

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2407/P

SUPERINTENDENCIA DE INDUSTRIA Y
DIVISIÓN DE NUEVAS CREACIONES

E. S. D.

SUPERINDUSTRIA Y COMERCIO
Radicación : 00097143 00000002 Folios: 134
Fecha (AMD): 2001-03-20 15:54:00
Tramite : 002 PATENTES D 1 REGISTRO/ 329 COMPLETAR
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Re: Expediente No. 00.097.143
Solicitud de Patente en nombre de
ORTHO - MCNEIL PHARMACEUTICAL, INC.

Yo, JIMENA ESCOBAR URIBE, identificada como aparece al pie de mi firma, domiciliada en Bogotá, en la carrera 11 A No. 94-76 Of. 305, obrando como apoderada de la sociedad ORTHO - MCNEIL PHARMACEUTICAL, INC., solicitante de la patente de la referencia, anexo al presente memorial los siguientes documentos:

Copias certificadas de las solicitudes de Patente Números 60/172,923 y 09/729,342 presentadas en los Estados Unidos de América los días 21 de diciembre de 1999 y 5 de diciembre de 2000, respectivamente, con la debida traducción de lo pertinente, incluyendo el capítulo reivindicatorio. En relación con la solicitud de patente No. 09/729,342, me permito manifestar que nuestro cliente nos había informado que ésta se presentó el día 12/5/00, lo cual interpretamos como mayo 12, 2000 y no diciembre 12, 2000 como hemos debido entenderlo. Habida cuenta que este error es un error de interpretación no se afecta el derecho de prioridad reivindicado, pues era perfectamente válido reivindicar prioridad de una patente presentada el 12 de mayo de 2000. Con el fin de enmendar el error de interpretación en mención, anexo al presente nuevo extracto y tarjeta de propietarios, documentos en los cuales se ha realizado la correspondiente corrección.

A este mismo respecto, debe tenerse en cuenta que en la primera página de la copia en mención la Oficina de Patentes correspondiente certificó la fecha de presentación de esa solicitud, cumpliéndose de esta forma todos y cada uno de los requisitos establecidos en el inciso segundo del artículo 10 de la Decisión 486 de la Comisión de la Comunidad Andina.

Señor Superintendente,


JIMENA ESCOBAR URIBE
C.C.39.779.452 de usaquén
T.P. 68228

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**ESTADOS UNIDOS DE AMERICA
A TODOS AQUELLOS A QUIENES EL PRESENTE
LLEGUE:**

**DEPARTAMENTO DE COMERCIO DE LOS ESTADOS
UNIDOS
Oficina de Patentes y Marcas de los Estados Unidos**

Enero 8, 2001

La presente es para certificar que el anexo es una copia fiel de los registros de la Oficina de Patentes y Marcas de los Estados Unidos, de los documentos de la solicitud de patente identificada más adelante, que cumplieron con los requerimientos para concederse una fecha de presentación de acuerdo con 35 USC 111.

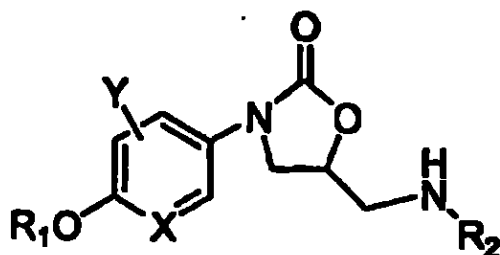
Número de Solicitud: 60/172,923

Fecha de Presentación: Diciembre 21, 1999

**Por la autoridad del
Comisionado de Patentes y Marca**

**(fdo) L. EDELEN
Oficial Certificador
Sello oficial de la Oficina de Patentes y Marcas de los
Estados Unidos de América**

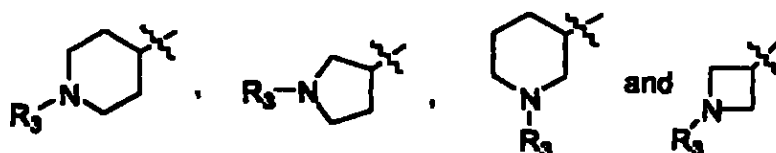
1. Un compuesto representado por la Formula I:



Formula I

En donde.

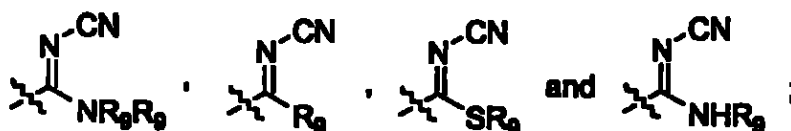
R1 se selecciona de



Donde

- R₃ se selecciona del grupo formado por H, alquil, -COR₄, -(CH₂)_theteroaril, -CHR₅R₆, -(CH₂)_t aril, -SO₂NR₅R₆, y -SO₂R₆;
- R₄ se selecciona del grupo formado por H, -OR₅, alquil, alquilaril, -(CH₂)_t aril, -(CH₂)_t heteroaril, -(CH₂)_t OR₅, -(CH₂)_tNR₇R₈, -CHR₅R₆ y -NR₅R₆, formando, opcionalmente, un derivado amino ciclico
- R₅ y R₆ se seleccionan independientemente del grupo formado por H, alquil, alquilaril, haloaril, -(CH₂)_t aril, -(CH₂)_t heteroaril, y amida;
- R₇ y R₈ se seleccionan independientemente del grupo formado por H, alquil, -COR₉, -SO₂R₉ y -CO₂R₉;
- R₉ se selecciona del grupo formado por H, alquil, aril y alquilaril;

R₂ se selecciona del grupo formado por C(O)N₉, C(O)OR₉



X es N o CH;

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Y se selecciona del grupo formado por H, halogeno, alcoxi, y alquil;

t es un numero entero entre 0 y 4;

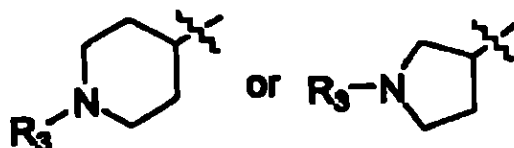
O un isómero óptico, enantiómero, diastómero, racemato o su mezcla racémica, o una de sus sales farmaceuticamente aceptables

2. El compuesto de la Reivindicación 1 en donde X es CH

3. El compuesto de la Reivindicación 1 donde R_2 es $-C(O)OR_9$ en donde R_9 es como es reivindica en la Reivindicación 1

4. El compuesto de la Reivindicación 3 en donde R_9 es H o alquil.

5. El compuesto de la Reivindicación 1 donde R_1 es



En donde R_3 es como se reivindica en la Reivindicación 1.

6. El compuesto de la Reivindicación 5 en donde R_3 se selecciona del grupo formado por $-COR_4$, $-SO_2R_9$ y $-(CH_2)_t$ heteroaril en donde R_4 , R_9 y t son como se reivindican en la Reivindicación 1

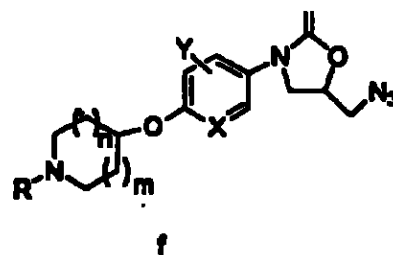
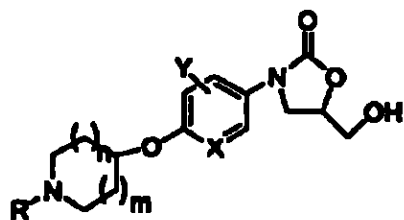
7. El compuesto de la Reivindicación 5 en donde R_4 se selecciona del grupo formado por $-OR_5$, alquil, $-(CH_2)_t$ aril, y $-(CH_2)_t$ heteroaril en donde R_5 y t son como se reivindica en la Reivindicación 1

8. El compuesto de la Reivindicación 7 en donde R_5 es alquil y R_9 es H o alquil.

9. Un compuesto de la Reivindicación 1 o una de sus sales farmaceuticamente aceptables, la cual es (S)-N-[[3-[3-fluoro-4-[N-(benciloxiacetamida) piperidinil-4-oxi]fenil-2-oxo-5-oxazolidinil] metil acetamida.

10. Un compuesto de la Reivindicación 1 o una de sus sales farmacéuticamente aceptables, la cual es (S)-N-[[3-[3-fluoro-4-(N-(-hidroxiacetamida) piperidinil-4-oxi)fenil]-2-oxo-5-oxazolidinil] metil] acetamida.
11. Un compuesto de la Reivindicación 1 o una de sus sales farmacéuticamente aceptables, la cual es (S)-N-[[3-[3-fluor-4-N-(metanosulfonamida) piperidinil-4-oxi]fenil]-2-oxo-5-oxazolidinil] metil]acetamida.
12. Un compuesto de la Reivindicación 1 o una de sus sales farmacéuticamente aceptables, la cual (S)-N-[[3-[3-fluoro-4-{N-(metilester)piperidinil- 4-oxi } fenil]-2-oxo-5-oxazolidinil] metil] acetamida.
13. Un compuesto de la Reivindicación 1 o una de sus sales farmacéuticamente aceptables, la cual es (S)-N-[[3-[3-fluoro-4- { N-(2-pirimidina)piperidinil-4-oxi}fenil] -2-oxo-5-oxazolidinil] metil] acetamida.
14. Un compuesto de la Reivindicación 1 o una de sus sales farmacéuticamente aceptables, la cual es (S)-N-[[3-[3-fluoro-4-{N-(3-cianobenzoilo)piperidinil-4-oxi } fenil]-2-oxo-5-oxazolidinil] metil] acetamida.
15. Un compuesto de la Reivindicación 1 o una de sus sales farmacéuticamente aceptables, la cual es (S)-N-[[3-[3-fluoro-4-{N-(5-ciano-2-piridil)piperidinil-4-oxi}fenil]-2-oxo-5-oxazolidinil] metil] acetamida.
16. Un compuesto de la Reivindicación 1 o una de sus sales farmacéuticamente aceptables, la cual es (S)-N-[[3-[3-fluoro-4-{N-(2-tiofenilcarbonil)piperidinil-4-oxi}fenil]-2-oxo-5-oxazolidinil] metil] acetamida.
17. Un compuesto de la Reivindicación 1 o una de sus sales farmacéuticamente aceptables, la cual (S)-N-[[3-[3-fluoro-4-{N-(-hidroxiacetamida)piperidinil-3-oxi } fenil]-2-oxo-5-oxazolidinil] metil] acetamida.

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18. Un compuesto de la Reivindicación 1 o una de sus sales farmaceuticamente aceptables, la cual (S)-N-[[3-[3-Fluoro-4-(N-(benciloxiacetamida)pirrolidinil-3-oxi } fenil]-2-oxo-5-oxazolidinil] metil]acetamida.
 19. Una composición farmacéutica que comprende un compuesto de la Reivindicación 1 y un agente de carga farmaceuticamente aceptable
 20. Un método para el tratamiento de un sujeto que presenta una condición causada o contribuida por una infección bacterial, el cual comprende la administración a dicho sujeto de una cantidad terapéuticamente efectiva del compuesto de la Formula I tal como se definió en la Reivindicación 1
 21. Un método para prevenir que un sujeto sufra de una condición causada o contribuida por una infección bacterial, el cual comprende la administración a dicho sujeto de una cantidad profilácticamente efectiva del compuesto de la Formula I tal como se definió en la Reivindicación 1
 22. El método de la Reivindicación 20 o 21 en donde dicha condición se selecciona del grupo formado por neumonía adquirida en comunidad, infecciones tracto respiratorias altas y bajas, infecciones de tejido blando y de piel, infecciones de huesos y ligamentos, e infecciones de pulmones adquiridas en hospital.
 23. El método de la reivindicación 20 o 21 en donde dicha bacteria se selecciona a partir del grupo formado por *S. aureus*, *S. epidermidis*, *S. pneumonias*, *Enterococcus spp.*, *Moraxella catarrhalis* y *H. influenzae*.
 24. El método de la Reivindicación 20 o 21 en donde dicha bacteria es un *Gram-positive coccus*.
 25. El método de la reivindicación 24 donde dicho *Gram-positive coccus* es resistente al antibiótico.
 26. Un intermedio de la Formula e o f



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En donde

R es Boc, $-\text{CH}(\text{Ph})_2$ o $-\text{COCH}_2\text{OCH}_2\text{Ph}$;

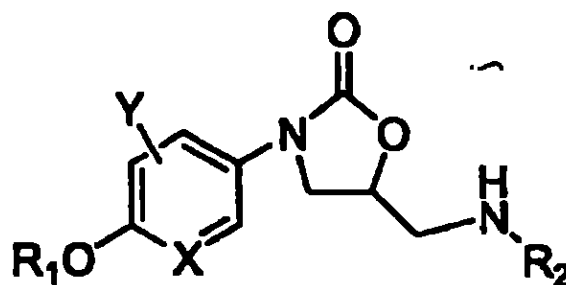
X es N o CH;

Y se selecciona del grupo formado por H, halógeno, alcoxi, y alquil;

n es 0, 1 o 2; y

m es 0 o 1.

27. Un proceso para la preparación de un compuesto representado por la formula I

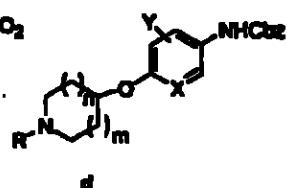
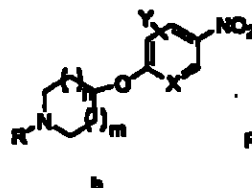
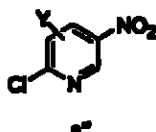
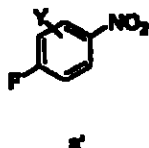


Formula I

En donde R_1 , R_2 , X y Y son como se reivindica en la Reivindicación 1 y R, m, y n son como se reivindica en la Reivindicación 26, cuyo proceso comprende:

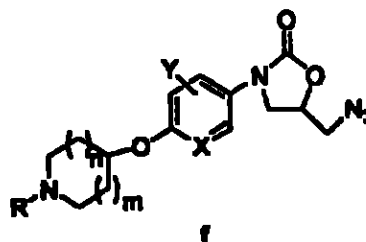
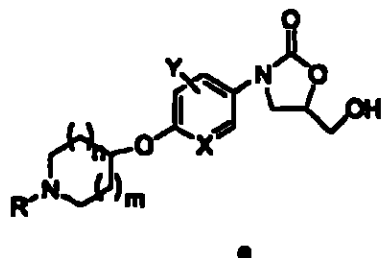
- a) La reacción de un compuesto representado por la Formula a con un compuesto representado por la Formula a' o a'' para formar un compuesto representado por la Formula b;

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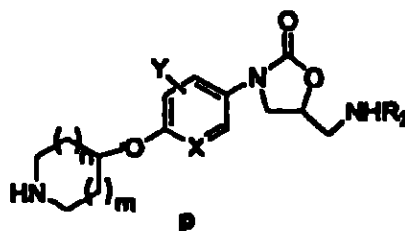
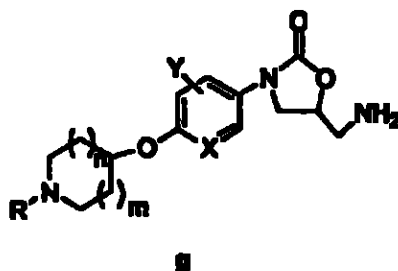
b) La conversión del compuesto representado por la Formula b en un compuesto representado por la Formula d:

c) La reacción del compuesto representado por la Formula d con para formar un compuesto representado por la Formula e:



d) La conversión del compuesto representado por la Formula e en un compuesto representado por la Formula f,

e) La conversión del compuesto representado por la Formula f en un compuesto representado por la Formula g;

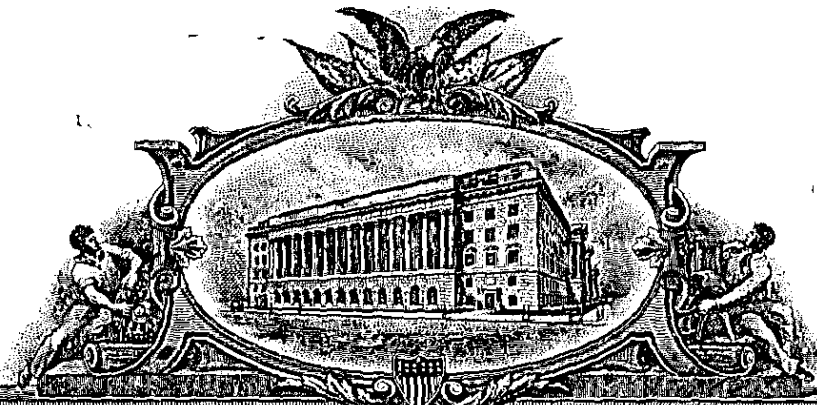


f) La conversión del compuesto representado por la Formula f a un compuesto representado por la Formula g; y

g) La conversión del compuesto representado por la Formula p a un compuesto representado por la Formula l;

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PA 346461



THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

January 08, 2001

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 UNDER 35 USC 111.

APPLICATION NUMBER: 60/172,923

FILING DATE: December 21, 1999



By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

L. Edelen

L. EDELEN
Certifying Officer

12-22-99

AIPKOV

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PROVISIONAL APPLICATION COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION under 37 CFR 1.53 (c).

DOCKET NUMBER		ORT-1073		TYPE A PLUS SIGN (+) INSIDE THIS BOX →		+		
INVENTOR(s) / APPLICANT(s)								
LAST NAME		FIRST NAME		MIDDLE INITIAL	RESIDENCE (CITY AND EITHER STATE OR FOREIGN COUNTRY)			
Wells-Weidner		Michele			12 Nore Dr., Neshanic Station, NJ 08853			
Boggs		Christine			53B Elwood Ave, Flemington, NJ 08822			
Hlasta		Dennis			5008 Davis Dr., Doylestown, PA 18901			
Nelson		Erin			805 Rt 202, Neshanic Station, NJ 08853			
TITLE OF THE INVENTION (250 characters max)								
PIPERIDINOL AND PYRROLIDINOL OXAZOLIDINONE ANTIBACTERIALS								
CORRESPONDENCE ADDRESS								
Audley A. Ciamporero, Jr., Johnson & Johnson, One Johnson & Johnson Plaza, New Brunswick								
STATE	New Jersey		ZIP CODE	08933-7003		COUNTRY	USA	
ENCLOSED APPLICATION PARTS (check all that apply)								
☒	Specification	Number of Pages	73	☐	Small Entry Statement			
☒	Claims	Number of Claims	27	☐	Other (specify)			
☐	Drawing(s)	Number of Sheets						
METHOD OF PAYMENT (check one)								
☐ A check or money order is enclosed to cover the Provisional filing fees.				Provisional Filing Fee Amount (\$)	\$ 150.00			
☒ The Commissioner is hereby authorized to charge filing fees and credit Deposit Account No. 10-0750/ORT1073/KJD								

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:

Respectfully submitted,

SIGNATURE	<i>Kenneth J. Dow</i>	Date: December 21, 1999
TYPED or PRINTED NAME	Kenneth J. Dow	REGISTRATION NO. 32,890

☐ Additional inventors are being named on separately numbered sheets attached hereto.

PROVISIONAL APPLICATION FILING ONLY

Telephone No. (732) 524-2641

Facsimile No. (732) 524-2808

Piperidinol and Pyrrolidinol Oxazolidinone Antibacterials

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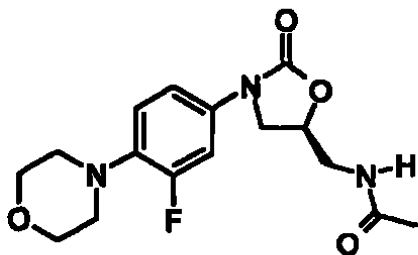
FIELD OF THE INVENTION

The present invention relates to the field of piperidinol, pyrrolidinol and azetidinol oxazolidinone compounds having antibacterial activity, pharmaceutical compositions containing the compounds, and methods of treating bacterial infections with the compounds.

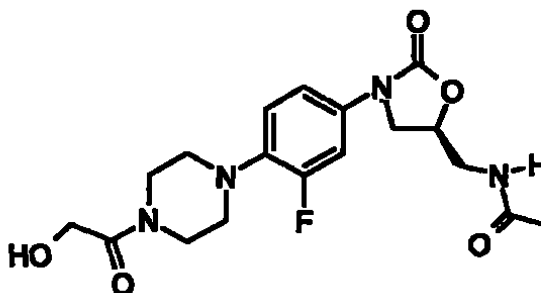
BACKGROUND OF THE INVENTION

Oxazolidinones have been identified, within the last twenty years, as a new class of antibacterials which are active against numerous multidrug-resistant gram positive organisms. Particularly problematic pathogens include methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE) and penicillin- and cephalosporin-resistant *Streptococcus pneumoniae*. As a class oxazolidinones exhibit a unique mechanism of action. Studies have shown that these compounds selectively bind to the 50S ribosomal subunit and inhibit bacterial translation at the initiation phase of protein synthesis. Exemplary members of oxazolidinones are linezolid (see WO 95/07271) and eperezolid.

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linezolid



eperezolid

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The following references relate to various oxazolidinone type compounds disclosed as having antibacterial activity:

U.S. Pat. No. 4,705,799 to W. A. Gregory discloses aminomethyl oxoxazolidinyl benzene derivatives, including the sulfides, sulfoxides, sulfones and sulfonamides, such as (1)-N-[3-[4-(methylsulfinyl)-phenyl]-2-oxoxazolidin-5-ylmethyl]acetamide.

U.S. Pat. No. 5,565,571 to Barbachyn et al. discloses substituted aryl- and heteroarylphenyloxazolidinones.

U.S. Pat. No. 5,792,765 to Riedl et al. relates to new substituted oxazolidinones.

U.S. Pat. No. 5,910,504 to Hutchinson discloses phenyloxazolidinone compounds having a nitrogen containing hetero-aromatic ring substitution attached through one of the nitrogen atoms.

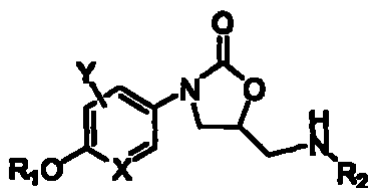
WO 93/09103 (Barbachyn et al.) discloses substituted aryl- and heteroarylphenyloxazolidinones.

WO 95/07271 (Barbachyn et al.) discloses oxazine and thiazine oxazolidinone derivatives.

WO 98/54161 (Hester et al.) provides oxazolidinone antibacterial agents having a thlocarbonyl functionality.

SUMMARY OF THE INVENTION

The invention provides new piperidinol, pyrrolidinol and azetidinol compounds of Formula I

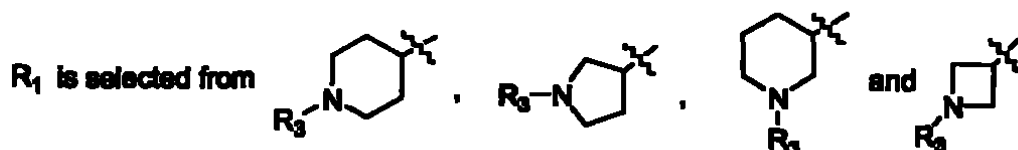


Formula I

wherein

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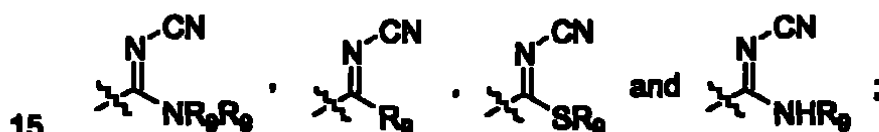
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wherein

- (a) R_1 is selected from H, alkyl, $-\text{COR}_4$, $-(\text{CH}_2)_t$ heteroaryl, $-\text{CHR}_4\text{R}_5$, $-(\text{CH}_2)_t$ aryl, $-\text{SO}_2\text{NR}_5\text{R}_6$, and $-\text{SO}_2\text{R}_6$;
- 5 (b) R_4 is selected from H, $-\text{OR}_6$, alkyl, alkylaryl, $-(\text{CH}_2)_t$ aryl, $-(\text{CH}_2)_t$ heteroaryl, $-(\text{CH}_2)_t\text{OR}_6$, $-(\text{CH}_2)_t\text{NR}_7\text{R}_8$, $-\text{CHR}_6\text{R}_9$, and $-\text{NR}_6\text{R}_9$, optionally forming a cyclic amino derivative;
- (c) R_5 and R_6 are independently selected from H, alkyl, alkylaryl, haloaryl, $-(\text{CH}_2)_t$ aryl, $-(\text{CH}_2)_t$ heteroaryl, and amido;
- 10 (d) R_7 and R_8 are independently selected from H, alkyl, $-\text{COR}_6$, $-\text{SO}_2\text{R}_6$ and $-\text{CO}_2\text{R}_6$; and
- (e) R_9 is selected from H, alkyl, aryl and alkylaryl;

R_2 is selected from $\text{C}(\text{O})\text{R}_9$, $\text{C}(\text{O})\text{OR}_9$,



X is N or CH;

Y is selected from H, halogen, alkoxy, and alkyl;

- 20 t is an integer of 0 to 4;

and optical isomers, enantiomers, diastereomers, racemates or racemic mixtures thereof, and pharmaceutically acceptable salts thereof.

- 25 Compounds of the above formula are useful as antibacterial agents for the treatment of bacterial infections in a subject such as human and animal.

- 30 The present invention is also directed to a method of treating a subject having a condition caused by or contributed to by bacterial infection, which comprises administering to said subject a therapeutically effective amount of the compound of Formula I.

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The present invention is further directed to a method of preventing a subject from suffering from a condition caused by or contributed to by bacterial infection, which comprises administering to the subject a prophylactically effective amount of the compound of Formula I.

Other objects and advantages will become apparent to those skilled in the art from a review of the ensuing specification.

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DETAILED DESCRIPTION

Relative to the above description, certain definitions apply as follows.

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Unless otherwise noted, under standard nomenclature used throughout this disclosure the terminal portion of the designated side chain is described first, followed by the adjacent functionality toward the point of attachment.

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Unless specified otherwise, the terms "alkyl", "alkenyl", and "alkynyl," whether used alone or as part of a substituent group, include straight and branched chains having 1 to 8 carbon atoms, or any number within this range. For example, alkyl radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl, 3-(2-methyl)butyl, 2-pentyl, 2-methylbutyl, neopentyl, n-hexyl, 2-hexyl and 2-methylpentyl. "Alkoxy" radicals are oxygen ethers formed from the previously described straight or branched chain alkyl groups. "Cycloalkyl" groups contain 3 to 8 ring carbons and preferably 5 to 7 ring carbons. The alkyl group and alkoxy group may be independently substituted with one or more members of the group including, but not limited to, mono-, di-, tri-, or per-halogen, alkyl, alkoxy, aryl, amino, OH, CN, mercapto, nitro, and C₁₋₈ acyloxy.

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The term "acyl" as used herein, whether used alone or as part of a substituent group, means an organic radical having 2 to 6 carbon atoms

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(branched or straight chain) derived from an organic acid by removal of the hydroxyl group.

- The term "halo" or "halogen" means fluoro, chloro, bromo and iodo.
- 5 (Mono-, di-, tri-, and per-)halo-alkyl is an alkyl radical substituted by independent replacement of the hydrogen atoms thereon with halogen.

- "Aryl" or "Ar," whether used alone or as part of a substituent group, is a carbocyclic aromatic radical including, but not limited to, phenyl, 1- or 2-
- 10 naphthyl and the like. The carbocyclic aromatic radical may be substituted by independent replacement of 1 to 3 of the hydrogen atoms thereon with halogen, -OH, -CN, mercapto, nitro, amino, alkyl, -O-alkyl, -S-alkyl, -NH-alkyl, -N(alkyl)₂, (mono-, di-, tri-, and per-) halo-alkyl, formyl, -COR₆, -COOR₆, -CONHR₆, -CONR₆R₆, -SOR₆, -SO₂R₆, -SO₂NHR₆, -SO₂NR₆R₆, alkyl-COO,
- 15 alkyl-CONH, or carboxamide or a second aryl ring, wherein R₆ and R₆ are defined as hereinabove. Illustrative aryl radicals include, for example, phenyl, naphthyl, diphenyl, fluorophenyl, difluorophenyl, benzyl, benzoyloxyphenyl, carboethoxyphenyl, acetylphenyl, ethoxyphenyl, phenoxyphenyl, hydroxyphenyl, carboxyphenyl, trifluoromethylphenyl, methoxyethylphenyl,
- 20 acetamidophenyl, tolyl, xylyl, dimethylcarbamylphenyl and the like. "Ph" or "PH" denotes phenyl.

- Whenever the term "alkyl", "acyl", or "aryl" or either of their prefix roots appear in a name of a substituent (e.g., aralkyl, dialkylamino) it shall be
- 25 interpreted as including those limitations given above for "alkyl", "acyl", and "aryl." Designated numbers of carbon atoms (e.g., C₁₋₂) shall refer independently to the number of carbon atoms in an alkyl or cycloalkyl moiety or to the alkyl portion of a larger substituent in which alkyl appears as its prefix root.

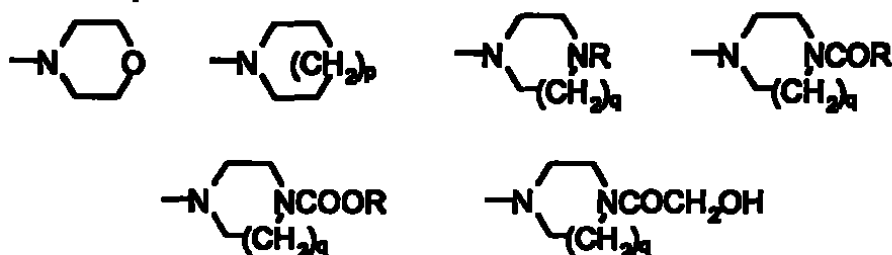
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Whether used alone or as part of a substituent group, "heteroaryl" refers to a cyclic aromatic radical having from five to ten ring atoms of which one ring atom is selected from S, O, and N; 0-2 ring atoms are additional

heteroatoms independently selected from S, O, and N; and the remaining ring atoms are carbon. The radical being joined to the rest of the molecule via any of the ring atoms, for example, pyridinyl, pyrazinyl, pyrimidinyl, pyrrolyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl, isoxazolyl, thiadiazolyl, triazolyl,

- 5 oxadiazolyl, thienyl, furanyl, quinolinyl, isoquinolinyl, and the like. The heteroaryl group may be substituted by independent replacement of 1 to 3 of the hydrogen atoms thereon with halogen, -OH, -CN, mercapto, nitro, amino, alkyl, -O-alkyl, -S-alkyl, -NH-alkyl, -N(alkyl)₂, (mono-, di-, tri-, and per-)halo-alkyl, formyl, -COR₂, -COOR₂, -CONHR₂, -CONR₂R₂, -SOR₂, -SO₂R₂, -
- 10 SO₂NHR₂, -SO₂NR₂R₂, alkyl-COO, alkyl-CONH, or carboxamide, wherein R₂ and R₃ are defined as hereinabove. Heteroaryl may also be substituted with a mono-oxo to give 4-oxo-1H-quinoline and the like.

- 15 A "cyclic amino" derivative is a 4 to 8 membered nitrogen containing cyclic group where the other remaining members are selected from carbon, nitrogen, oxygen or sulfur, for instance an azetidiny group, pyrrolidinyl group, piperidinyl group, morpholino group, piperazinyl, or groups of the following formulae:



- 20 wherein p is -2 to 4 and q is 1-4.

- 25 Unless specified otherwise, it is intended that the definition of any substituent or variable at a particular location in a molecule be independent of its definitions elsewhere in that molecule. It is understood that substituents and substitution patterns on the compounds of this invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art as well as those methods set forth herein.

The compounds of the instant invention are asymmetric in the oxazolidinone ring at the 5- position and thus exist as optical antipodes. As such, all possible optical antipodes, enantiomers or diastereomers resulting from additional asymmetric centers that may exist in optical antipodes, racemates and racemic mixtures thereof are also part of this invention. The antipodes can be separated by methods known to those skilled in the art such as, for example, fractional recrystallization of diastereomeric salts of enantiomerically pure acids. Alternatively, the antipodes can be separated by chromatography on a Pirkle column.

The phrase "a pharmaceutically acceptable salt" denotes salts of the free base which possess the desired pharmacological activity of the free base and which are neither biologically nor otherwise undesirable. These salts may be derived from inorganic or organic acids. Examples of inorganic acids are hydrochloric acid, nitric acid, hydrobromic acid, sulfuric acid, or phosphoric acid. Examples of organic acids are acetic acid, propionic acid, glycolic acid, lactic acid, pyruvic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, methyl sulfonic acid, salicylic acid and the like. Suitable salts are furthermore those of inorganic or organic bases, such as KOH, NaOH, $\text{Ca}(\text{OH})_2$, $\text{Al}(\text{OH})_3$, piperidine, morpholine, ethylamine, triethylamine and the like.

Also included within the scope of the invention are the hydrated forms of the compounds which contain various amounts of water, for instance, the hydrate, hemihydrate and sesquihydrate forms.

The term "subject" includes, without limitation, any animal or artificially modified animal. As a particular embodiment, the subject is a human.

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The term "drug-resistant" or "drug-resistance" refers to the characteristics of a microbe to survive in presence of a currently available antimicrobial agent such as an antibiotic at its routine, effective concentration.

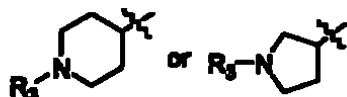
5 The compounds described in the present invention possess antibacterial activity due to their novel structure, and are useful as antibacterial agents for the treatment of bacterial infections in humans and animals.

10 In particular, compounds of Formula I wherein X is CH are embodiments of the present invention for such purposes.

15 Compounds of Formula I wherein R_2 is $C(O)OR_6$ wherein R_6 is as described above are particular embodiments of this invention.

More particularly, compounds of Formula I wherein R_6 is H or alkyl are also embodiments of this invention.

Compounds of Formula I wherein R_1 is



20 wherein R_3 is as described above are further particular embodiments of this invention.

25 More particularly, compounds of Formula I wherein R_3 is selected from $-COR_4$, $-SO_2R_5$ and $(CH_2)_t$ heteroaryl wherein R_4 , R_5 and t are as described above are embodiments of this invention.

Still more particularly, compounds of Formula I wherein R_4 is selected from $-OR_6$, alkyl, $-(CH_2)_t$ aryl, and $-(CH_2)_t$ heteroaryl wherein R_6 and t are as described above are embodiments of this invention.

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The following are yet other particular embodiments of the present invention for such purposes:

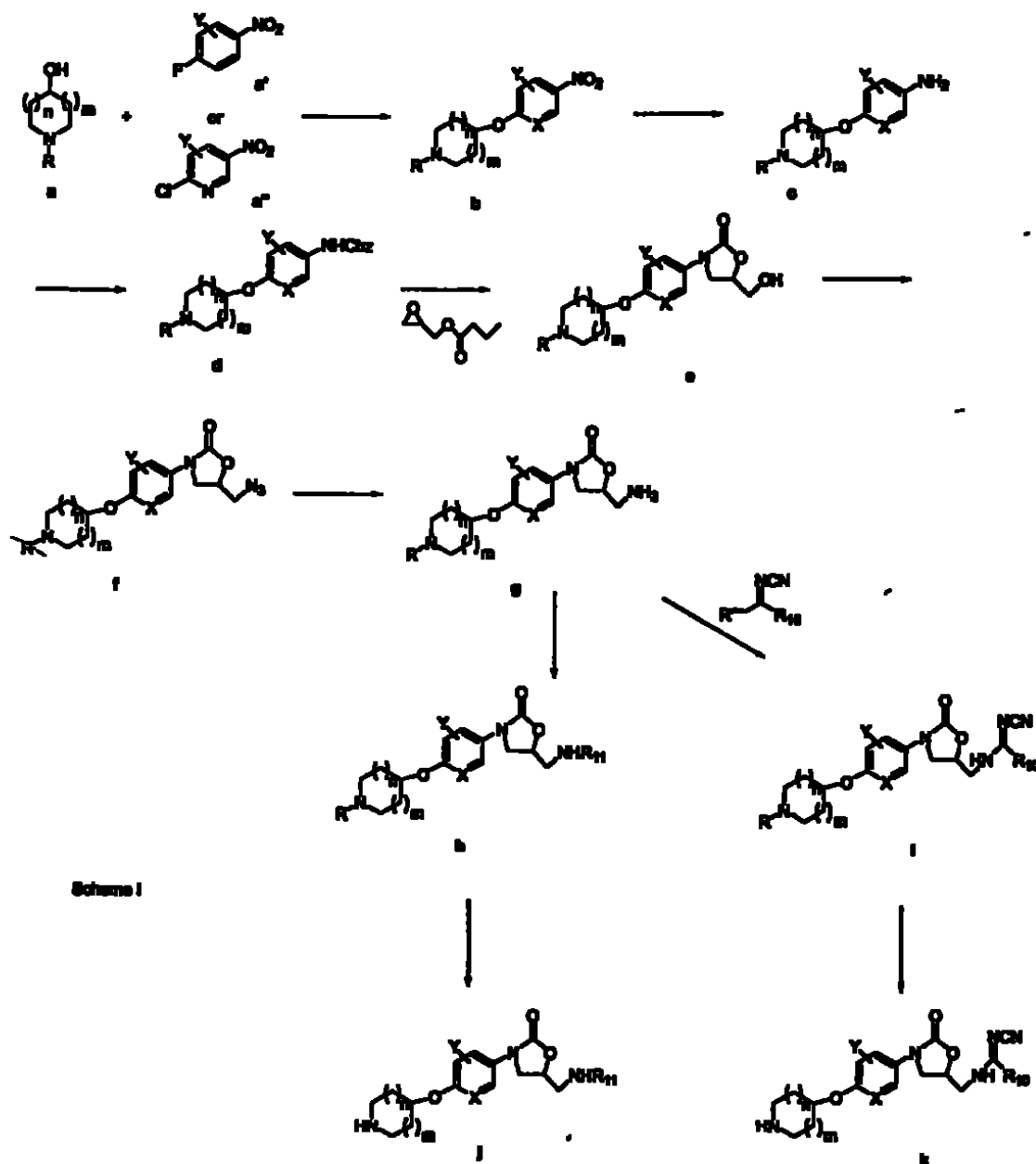
- 5 (S)-N-[[3-[3-fluoro-4-[N-(benzyloxyacetamide)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
- (S)-N-[[3-[3-fluoro-4-[N-(α -hydroxyacetamide)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
- (S)-N-[[3-[3-fluoro-4-[N-(methanesulfonamide)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
- 10 (S)-N-[[3-[3-fluoro-4-[N-(methyl ester)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
- (S)-N-[[3-[3-fluoro-4-[N-(2-pyrimidine)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
- (S)-N-[[3-[3-fluoro-4-[N-(3-cyanobenzoyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
- 15 (S)-N-[[3-[3-fluoro-4-[N-(5-cyano-2-pyridyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
- (S)-N-[[3-[3-fluoro-4-[N-(2-thiophenylcarbonyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
- 20 (S)-N-[[3-[3-fluoro-4-[N-(α -hydroxyacetamide)piperidinyl-3-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide; and
- (S)-N-[[3-[3-Fluoro-4-[N-(benzyloxyacetamide)pyrrolidinyl-3-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

25

This invention also provides processes for preparing the instant compounds. The compounds of Formula I may be prepared from readily available starting materials such as known oxazolidinone intermediates in accordance with synthetic methods well known in the art. The following are representative procedures outlined in Schemes I and II:

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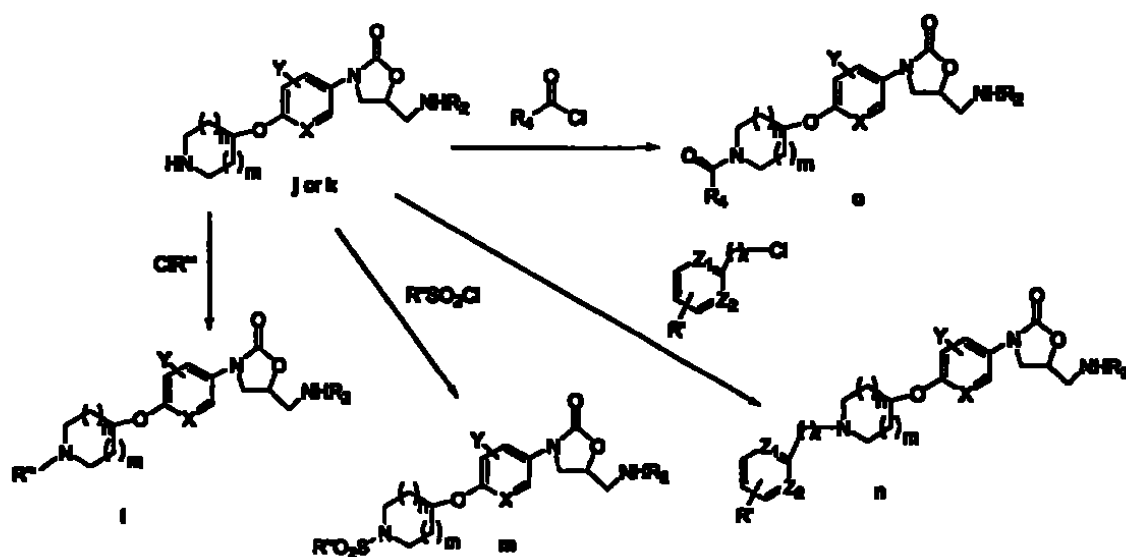


Scheme I

In accordance with Scheme I, wherein R is Boc, $-\text{CH}(\text{Ph})_2$ or $-\text{COCH}_2\text{OCH}_2\text{Ph}$, R_{11} is $-\text{COR}_9$ or $-\text{CO}_2\text{R}_9$, R' is any of the substituents on an aryl or heteroaryl group as described above, R'' is R_9 and $-\text{NR}_9\text{R}_9$, R''' is alkyl, substituted alkyl and $-\text{CHR}_9\text{R}_9$, Z_1 and Z_2 are independently N or CH, n is 0, 1 or 2 and m is 0 or 1, R'''' is $-\text{SCH}_3$ or $-\text{OCH}_3$, R_{10} is $-\text{NR}_9\text{R}_9$, R_9 , $-\text{SR}_9$, or $-\text{NHR}_9$, and X, Y, R_4 , R_5 , R_6 , R_7 , and t are as described above, an appropriately substituted halo-nitrobenzene such as that of Formula a' or an appropriately substituted halo-nitropyridine such as that of Formula a'' is added to a compound of Formula a (all of which are either commercially available or may be readily prepared by known methods) in acetone, dimethylformamide (DMF), or tetrahydrofuran (THF). The mixture is treated with an appropriate base such as potassium t-butoxide (KOtBu) to obtain the corresponding compound of Formula b. The compound of Formula b may be reduced to the corresponding compound of Formula c under appropriate conditions such as H_2 , Pd/C and ethanol (EtOH) or NH_4COOH , Pd/C and methanol (MeOH). Then compound c is treated with benzylchloroformate (CbzCl) in the presence of an appropriate base such as cesium carbonate (CsCO_3) in an appropriate solvent such as THF, H_2O or acetone to obtain the corresponding compound of Formula d. Compound d is then treated with an appropriate base such as nBuLi, followed by addition of glycidal butyrate in an appropriate solvent such as THF to obtain the corresponding compound of Formula e. The compound of Formula e is treated with methanesulfonyl chloride (MsCl) and an appropriate base such as triethylamine (NEt_3) in an appropriate solvent such as methylene chloride (CH_2Cl_2). After standard workup, sodium azide (NaN_3) is then added into the mixture in an appropriate solvent such as dimethylformamide (DMF) and heated at a preferred temperature range of 70°C to 90°C to obtain the corresponding compound of Formula f. The compound of Formula f may be reduced under appropriate conditions such as H_2 and Pd/C in an appropriate solvent such as ethyl acetate (EtOAc), or the compound of Formula f may be reduced using triphenylphosphine (PPh_3) and THF/ H_2O to obtain the corresponding compound of Formula g.

- The compound of Formula g can be treated with an appropriate acylating agent such as acetic anhydride (Ac_2O) or acetyl chloride (AcCl), along with an appropriate base such as pyridine or NEt_3 to give the corresponding compound of Formula h. The compound of Formula g can also be treated with an appropriate imine to give the corresponding compound of Formula i. Compounds j and k can be obtained independently from compounds h and i by deprotection with either trifluoroacetic acid (TFA) in an appropriate solvent such as CH_2Cl_2 or with Pd/C in an appropriate solvent such as EtOH or EtOAc to obtain the corresponding compounds of Formulae j and k.

Compounds of Formulae l through o may be obtained in accordance with different routes as shown in Scheme II:

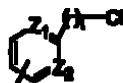


Scheme II

- The compound of Formula j or k can be treated with an appropriate alkylating agent represented by ClR^m in the presence of an appropriate base such as NEt_3 in an appropriate solvent such as CH_2Cl_2 or THF to obtain the corresponding compound of Formula l. Alternatively, the compound of Formula j or k can be treated with an appropriate sulfonyl chloride represented by $\text{R}^3\text{SO}_2\text{Cl}$ such as MsCl in the presence of an appropriate base such as NEt_3 in an appropriate solvent such as CH_2Cl_2 or THF to obtain the

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corresponding compound of Formula m. Still alternatively, the compound of Formula j or k can be treated with an appropriate alkylating agent



represented by R in the presence of an appropriate base such as NEt_3 in an appropriate solvent such as CH_2Cl_2 or THF to obtain the corresponding compound of Formula n. Finally, the compound of Formula j or k can also be treated with an appropriate acylating agent represented by R_4COCl such as $AcCl$ in the presence of an appropriate base such as NEt_3 in an appropriate solvent such as CH_2Cl_2 or THF to obtain the corresponding compound of Formula o. In several cases, R_4 contains a protected amine or protected alcohols moiety. After removal of the protecting group, the resulting amine or alcohol can be further derivatized.

These compounds have antimicrobial activity against susceptible and drug resistant *S. aureus*, *S. epidermidis*, *S. pneumoniae*, *E. faecalis*, *E. faecium*, *Moraxella catarrhalis* and *H. influenzae*. These compounds are particularly useful against drug resistant Gram positive cocci such as methicillin-resistant staphylococci and vancomycin-resistant enterococci. These compounds are useful in the treatment of community-acquired pneumonia, upper and lower respiratory tract infections, skin and soft tissue infections, hospital-acquired lung infections, bone and joint infections, and other bacterial infections.

Minimal inhibitory concentration (MIC) has been an indicator of in vitro antibacterial activity widely used in the art. The in vitro antimicrobial activity of the compounds was determined by the microdilution broth method following the test method from the National Committee for Laboratory Standards (NCCLS). This method is described in the NCCLS Document M7-A4, Vol.17, No.2, "Methods for Dilution Antimicrobial Susceptibility Test for Bacteria that Grow Aerobically—Fourth Edition", which is incorporated herein by reference.

In this method two-fold serial dilutions of drug in cation adjusted Mueller-Hinton broth are added to wells in microdilution trays. The test

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organisms are prepared by adjusting the turbidity of actively growing broth cultures so that the final concentration of test organism after it is added to the wells is approximately 5×10^4 CFU/well.

- 5 Following inoculation of the microdilution trays, the trays are incubated at 35 °C for 16-20 hours and then read. The MIC is the lowest concentration of test compound that completely inhibits growth of the test organism. The amount of growth in the wells containing the test compound is compared with the amount of growth in the growth-control wells (no test compound) used in
- 10 each tray. As set forth in Table 1, compounds of the present invention were tested against a variety of Gram positive and Gram negative pathogenic bacteria resulting in a range of activities, from 1 to ≥ 128 $\mu\text{g/mL}$ depending on the organism tested.

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Table 1. MIC Values of Some Compounds of Formula I

Com- pound No.	MIC (µg/mL)			Com- pound No.	MIC (µg/mL)		
	<i>E. faecium</i> OC3312	MRSA OC 2878	<i>S. aureus</i> Broth		<i>E. faecium</i> OC3312	MRSA OC 2878	<i>S. aureus</i> Broth
1	>32	16	32	26	16	8	16
2	8	32	8	27	16	16	16
3	4	2	4	28	16	8	16
4	8	4	4	29	32	16	32
5	16	8	8	30	16	8	16
6	8	4	4	31	32	16	16
7	16	8	8	32	32	8	16
8	8	4	8	33	32	16	16
9	8	4	4	34	>128	64	128
10	32	16	16	35	64	32	32
11	16	8	16	36	16	8	8
12	16	8	8	37	16	8	8
13	16	8	8	38	32	8	16
14	8	4	4	39	16	16	16
15	8	8	8	40	16	8	4
16	32	32	32	41	>128	64	128
17	16	16	8	42	>128	32	32
18	64	16	8	43	>128	128	128
19	32	32	16	44	128	64	32
20	16	8	8	45	128	64	64
21	64	32	32	46	>128	64	64
22	8	4	8	47	>128	64	64
23	16	4	16	48	>128	32	64
24	32	16	8	49	>128	128	> 64
25	64	32	32	50	>64	64	>64

5 This invention further provides a method of treating bacterial infections, or enhancing or potentiating the activity of other antibacterial agents, in warm-blooded animals, which comprises administering to the animals a compound

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of the invention alone or in admixture with another antibacterial agent in the form of a medicament according to the invention.

When the compounds are employed for the above utility, they may be combined with one or more pharmaceutically acceptable carriers, e.g., solvents, diluents, and the like, and may be administered orally in such forms as tablets, capsules, dispersible powders, granules, or suspensions containing for example, from about 0.5% to 5% of suspending agent, syrups containing, for example, from about 10% to 50% of sugar, and elixirs containing, for example, from about 20% to 50% ethanol, and the like, or parenterally in the form of sterile injectable solutions or suspensions containing from about 0.5% to 5% suspending agent in an isotonic medium. These pharmaceutical preparations may contain, for example, from about 0.5% up to about 90% of the active ingredient in combination with the carrier, more usually between 5% and 60% by weight.

Compositions for topical application may take the form of liquids, creams or gels, containing a therapeutically effective concentration of a compound of the invention admixed with a dermatologically acceptable carrier.

In preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed. Solid carriers include starch, lactose, dicalcium phosphate, microcrystalline cellulose, sucrose and kaolin, while liquid carriers include sterile water, polyethylene glycols, non-ionic surfactants and edible oils such as corn, peanut and sesame oils, as are appropriate to the nature of the active ingredient and the particular form of administration desired. Adjuvants customarily employed in the preparation of pharmaceutical compositions may be advantageously included, such as flavoring agents, coloring agents, preserving agents, and antioxidants, for example, vitamin E, ascorbic acid, BHT and BHA.

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5 The preferred pharmaceutical compositions from the standpoint of ease of preparation and administration are solid compositions, particularly tablets and hard-filled or liquid-filled capsules. Oral administration of the compounds is preferred. These active compounds may also be administered parenterally or intraperitoneally. Solutions or suspensions of these active compounds as a free base or pharmacological acceptable salt can be prepared in water suitably mixed with a surfactant such as hydroxypropyl-cellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations may contain a preservative to prevent the growth of microorganisms.

15 The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils.

25 The effective dosage of active ingredient employed may vary depending on the particular compound employed, the mode of administration and the severity of the condition being treated. However, in general, satisfactory results are obtained when the compounds of the invention are administered at a daily dosage of from about 0.1 mg/kg to about 400 mg/kg of animal body weight, preferably given in divided doses two to four times a day, or in sustained release form. For most large mammals the total daily dosage is from about 0.07 g to 7.0 g, preferably from about 100 mg to 1000 mg. Dosage forms suitable for internal use comprise from about 100 mg to 500 mg of the active compound in intimate admixture with a solid or liquid pharmaceutically acceptable carrier. This dosage regimen may be adjusted

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to provide the optimal therapeutic response. For example, several divided doses may be administered daily or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic situation.

5 The production of the above-mentioned pharmaceutical compositions and medicaments is carried out by any method known in the art, for example, by mixing the active ingredient(s) with the diluent(s) to form a pharmaceutical composition (e.g. a granulate) and then forming the composition into the medicament (e.g. tablets).

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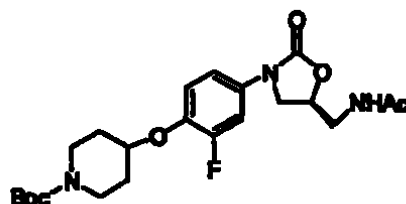
The following examples describe in detail the chemical synthesis of representative compounds of the present invention. The procedures are illustrations, and the invention should not be construed as being limited by chemical reactions and conditions they express. No attempt has been made to optimize the yields obtained in these reactions, and it would be obvious to one skilled in the art that variations in reaction times, temperatures, solvents, and/or reagents could increase the yields.

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Example 1

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(S)-N-[[3-[3-Fluoro-4-(N-(t-butoxycarbonyl)-4-piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide



Compound 1

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N-(t-Butoxycarbonyl)-4-piperidinol;

To a solution of 25 g (247 mmol) 4-piperidinol in 350 mL dry tetrahydrofuran (THF) at 0°C was added dropwise 60.2 g (276 mmol) di-*t*-butylcarbonate in 350 mL dry THF. The reaction was allowed to warm to room temperature (rt) and stirred overnight. The solvent was removed under reduced pressure, the resulting residue dissolved in 700 mL CH₂Cl₂ and the

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solution extracted with H₂O (1 x 400 mL), dried over MgSO₄, filtered and rotary evaporated to yield 45 g (91%) of N-(t-butoxycarbonyl)-4-piperidinol as an oil which slowly solidified to white crystals. ¹H NMR (CDCl₃) δ 3.75-3.96 (m, 3H); 2.92-3.13 (m, 2H); 1.80-1.93 (m, 4H); and 1.48 (s, 9H).

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1-[N-(t-Butoxycarbonyl)piperidinyl-4-oxyl]-2-fluoro-4-nitrobenzene:

To a solution of 740 mg (3.7 mmol) of N-(t-butoxycarbonyl)-4-piperidinol in 10 mL dry THF at 0°C was added dropwise 4 mL (4.0 mmol) 1M KOtBu. After stirring at 0°C for 0.5 h, 0.40 mL (3.6 mmol) 3,4-difluoronitrobenzene was added and the reaction warmed to rt and stirred overnight. The reaction was poured into 100 mL H₂O and extracted with CH₂Cl₂ (3 x 100 mL). The combined aqueous layers were washed with H₂O, dried with MgSO₄, filtered, and the solvent removed by rotary evaporation. Then the solid was triturated with cold hexanes to afford 1.1 g (89%) of 1-[N-(t-butoxycarbonyl)piperidinyl-4-oxyl]-2-fluoro-4-nitrobenzene as a pale yellow solid; mp 88-90°C, MS (CI) [M+Na]⁺ 364.

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1-[4-(N-t-Butoxycarbonyl)piperidinyl-4-oxyl]-2-fluoro-4-aminobenzene:

To 1.78 g (5.23 mmol) of 1-[N-(t-butoxycarbonyl)piperidinyl-4-oxyl]-2-fluoro-4-nitrobenzene in 100 mL MeOH was added 1.05 g (18.8 mmol) ammonium formate and 70 mg 10% Pd/C and the reaction heated at reflux under N₂ for 2 h. The reaction was filtered through a pad of celite and the filtrate evaporated to afford crude aniline as a gold oil. The material was used without further purification in the next step.

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3-Fluoro-4-(N-(t-butoxycarbonyl)-4-piperidinyl)-1-(phenylmethoxy carbonylamino)benzene:

To 1-[4-(N-t-butoxycarbonyl)piperidinyl-4-oxyl]-2-fluoro-4-aminobenzene (5.23 mmol) in 150 mL 2:1 acetone:H₂O at 0°C was added 1.03 g (12.3 mmol) NaHCO₃ and 0.90 mL (6.30 mmol) benzylchloroformate. After stirring at rt for 8 h the volatiles were evaporated, the residue diluted with 300 mL H₂O and extracted with Et₂O (3 x 150 mL). The combined organic layers were washed with H₂O, dried over MgSO₄, filtered, and the

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solvent removed by rotary evaporation. Silica gel chromatography (20% EtOAc in Hexanes) afforded 2.06 g (89%) of 3-fluoro-4-(N-(t-butoxycarbonyl)-4-piperidinyl)-1-(phenylmethoxycarbonylamino) benzene as a yellow, waxy solid. ¹H NMR (CDCl₃) δ 7.3-7.4 (m, 6H); 6.9-7.0 (m, 2H); 6.60 (brs, 1H); 4.3-4.4 (m, 1H); 3.7-3.8 (m, 2H); 3.2-3.3 (m, 2H); 1.8-2.0 (m, 2H); 1.6-1.8 (m, 2H); and 1.48 (s, 9H).

(R)-[3-[3-Fluoro-4-(N-(t-butoxycarbonyl)-4-piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methanol:

10 To 1.73 g (3.89 mmol) of 3-fluoro-4-(N-(t-butoxycarbonyl)-4-piperidinyl)-1-(phenylmethoxycarbonylamino)benzene in 25 mL dry THF at -78°C was added 2 mL (5.0 mmol) 2.5M *n*-BuLi and the reaction stirred for 1 h. Then 0.71 mL (5.01 mmol) (R)-glycidyl butyrate was added via syringe and the reaction warmed to rt and stirred overnight. The reaction was carefully
15 poured into 150 mL sat. NH₄Cl (aq.) and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with H₂O, dried over MgSO₄, filtered, and the solvent removed by rotary evaporation. Silica gel chromatography (40% EtOAc in hexanes to 70% EtOAc in hexanes) gave 1.15 g (72%) of (R)-[3-[3-fluoro-4-(N-(t-butoxycarbonyl)-4-piperidinyl)phenyl]-
20 2-oxo-5-oxazolidinyl]methanol as a white solid; mp 110-111°C, MS (CI) [M+Na]⁺ 433.5.

(R)-[3-[3-Fluoro-4-(N-(t-butoxycarbonyl)-4-piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl methanesulfonate:

25 To 1.03 g (2.51 mmol) of (R)-[3-[3-fluoro-4-(N-(t-butoxycarbonyl)-4-piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methanol in 50 mL CH₂Cl₂ at 0°C was added 0.70 mL (5.02 mmol) NEt₃ and 0.37 mL (4.78 mmol) methanesulfonyl chloride. After stirring for 3 h at 0°C the reaction was poured into 75 mL H₂O and extracted with CH₂Cl₂ (100 mL). The combined organic layers were
30 washed with H₂O, dried over MgSO₄, filtered and the solvent removed by rotary evaporation to yield 1.21 g (99%) of (R)-[3-[3-fluoro-4-(N-(t-butoxycarbonyl)-4-piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl

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methanesulfonate as a cream solid; mp 127-128°C, MS (CI) [M+H-Boc]⁺ 389.2.

5 (R)-[3-[3-Fluoro-4-(N-(t-butoxycarbonyl)-4-piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methylazide:

To a solution of (R)-[3-[3-fluoro-4-(N-(t-butoxycarbonyl)-4-piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl methanesulfonate (5.20 mmol) in 70 mL dimethylformamide (DMF) was added 1.22 g (18.8 mmol) sodium azide and the reaction heated at 75°C overnight. Then the reaction was
10 poured into 300 mL H₂O and extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with H₂O (3 x 200 mL), dried over MgSO₄, filtered, and the solvent removed by rotary evaporation to yield 2.07 g (92%) of (R)-[3-[3-fluoro-4-(N-(t-butoxycarbonyl)-4-piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methylazide as a beige solid. ¹H NMR (CDCl₃) δ 7.46 (dd, J =
15 12.9 and 2.7 Hz, 1H); 7.14 (dt, J = 8.9 and 1.4 Hz, 1H); 7.01 (t, J = 8.9 Hz, 1H); 4.7-4.8 (m, 1H); 4.3-4.4 (m, 1H); 4.05 (t, J = 8.9 Hz, 1H); 3.83 (dd, J = 8.9 and 6.2 Hz, 1H); 3.7-3.8 (m, 2H); 3.71 (dd, J = 13.2 and 4.6 Hz, 1H); 3.59 (dd, J = 13.2 and 4.3 Hz, 1H); 3.2-3.3 (m, 2H); 1.8-2.0 (m, 2H); 1.7-1.8 (m, 2H); and 1.47 (s, 9H).

20 (S)-N-[3-[3-Fluoro-4-(N-(t-butoxycarbonyl)-4-piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methylacetamide (Compound 1):

To a solution of (R)-[3-[3-fluoro-4-(N-(t-butoxycarbonyl)-4-piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methylazide (5.20 mmol) in 9 mL dry
25 THF was added 1.51 g (5.75 mmol) triphenylphosphine and the reaction stirred for 3 h at rt. Then 4.5 mL H₂O was added and the reaction heated at 60°C for 4 h. The volatiles were evaporated and the residue extracted with benzene (2 x 20 mL) to yield the crude amine.

To a solution of this crude amine in 100 mL EtOAc was added 0.58 mL
30 (6.15 mmol) acetic anhydride and 1.2 mL (14.8 mmol) pyridine, and the reaction stirred at rt overnight. The reaction mixture was poured into 250 mL H₂O, extracted with EtOAc, dried over MgSO₄, filtered, and the solvent removed under reduced pressure. Silica gel chromatography (100% EtOAc

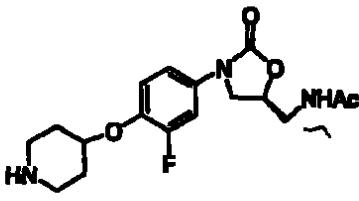
149-60

to 5% MeOH in EtOAc) yielded 1.85 g (79%) of (S)-N-[[3-[3-fluoro-4-(N-(t-butoxycarbonyl)-4-piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide as a white solid; mp 179-180°C, MS (CI) [M+Na]⁺ 474.

5

Example 2

(S)-N-[[3-[3-Fluoro-4-{piperidinyl-4-oxo}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide



Compound 2

10

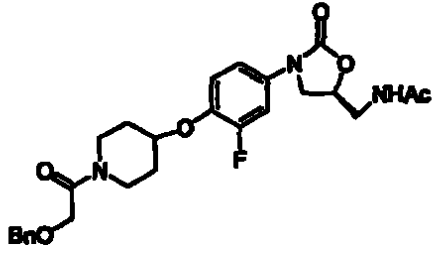
To a solution of 1.94 g (4.30 mmol) of Compound 1 in 225 mL CH₂Cl₂ was added 2.5 mL (32.5 mmol) trifluoroacetic acid (TFA) and the reaction stirred at rt for 6 h. The volatiles were evaporated under reduced pressure. The resulting oil (TFA salt) was dissolved in 100 mL H₂O, extracted with EtOAc (100 mL), and the aqueous layer was cooled to 0°C and basicified with 1N NaOH. This solution was extracted with EtOAc (5 x 200 mL), the combined extracts washed with brine, dried over MgSO₄, filtered, and evaporated under reduced pressure to yield (S)-N-[[3-[3-fluoro-4-(piperidinyl-4-oxo)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide as a pale yellow glass; mp 55-59°C, MS (CI) [M+H]⁺ 352.

15

20

Example 3

(S)-N-[[3-[3-Fluoro-4-(N-(benzyloxyacetamide)piperidinyl-4-oxo)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide



Compound 3

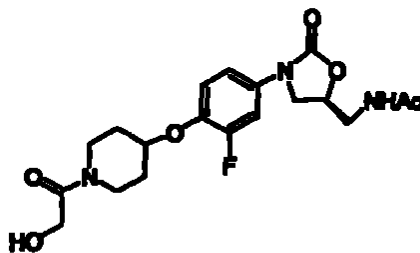
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To a suspension of Compound 2 (1.50 mmol) in 50 mL CH_2Cl_2 was added 0.60 mL (4.3 mmol) NEt_3 and 0.25 mL (1.58 mmol) benzyloxyacetyl chloride. After stirring for 18 h, the reaction was poured into 75 mL H_2O and extracted with CH_2Cl_2 (4 x 50 mL). The combined organic layers were dried over MgSO_4 , filtered, and evaporated under reduced pressure. Silica gel chromatography (5% MeOH in EtOAc) afforded (S)-N-[[3-[3-fluoro-4-(N-(benzyloxyacetamide)piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide as a white glass. ^1H NMR (CDCl_3) δ 7.47 (dd, $J = 12.9$ and 2.5 Hz, 1H); 7.3-7.4 (m, 5H); 6.96 (t, $J = 8.8$ Hz, 1H); 6.24 (brt, $J = 6.1$ Hz, 1H); 4.7-4.8 (m, 1H); 4.61 (s, 2H); 4.4-4.5 (m, 1H); 4.20 (s, 2H); 4.02 (t, $J = 9.0$ Hz, 1H); 3.6-3.8 (m, 6H); 3.4-3.5 (m, 1H); 2.02 (s, 3H); and 1.8-1.9 (m, 4H).

Example 4

(S)-N-[[3-[3-Fluoro-4-[N-(α -hydroxyacetamide)piperidinyl-4-oxy]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide



Compound 4

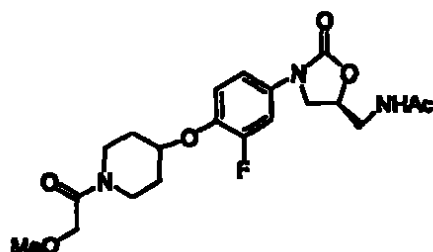
To a solution of 540 mg (1.08 mmol) of Compound 3 in 50 mL MeOH was added 503 mg ammonium formate and a catalytic amount of 10% Pd/C, and the reaction was heated at reflux overnight. Then the reaction was filtered through a pad of celite and the solvent removed under reduced pressure. Silica gel chromatography (2% to 10% MeOH in CH_2Cl_2) afforded (S)-N-[[3-[3-fluoro-4-[N-(α -hydroxyacetamide)piperidinyl-4-oxy]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide as a hygroscopic white foam (93%). ^1H NMR (CDCl_3) δ 7.49 (dd, $J = 12.9$ and 2.6 Hz, 1H); 7.09 (dd, $J = 8.9$ and 1.6 Hz, 1H); 7.00 (t, $J = 8.9$ Hz, 1H); 6.18 (brt, $J = 6.1$ Hz, 1H); 4.7-4.8 (m, 1H); 4.51

151 *JS*

(q, $J = 4.6$ Hz, 1H); 4.19 (s, 2H); 4.02 (t, $J = 9.0$ Hz, 1H); 3.5-3.8 (m, 7H); 3.20 (dt, $J = 13.7$ and 5.2 Hz, 1H); 2.03 (s, 3H); and 1.90 (m, 4H).

Example 5

5 (S)-N-[[3-[3-Fluoro-4-(N-(methoxyacetamide)piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

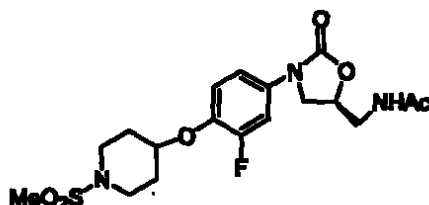


Compound 5

10 To a solution of (S)-N-[[3-[3-fluoro-4-(piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (0.756 mmol) in 30 mL EtOAc was added 1.0 mL (7.17 mmol) NEt_3 and methoxyacetylchloride (0.875 mmol). The reaction stirred at rt for 2.5 h, was poured into 50 mL H_2O , and extracted with EtOAc. The organic layer was washed with H_2O , dried over MgSO_4 , filtered, and the solvent removed by rotary evaporation to yield the impure amide. Silica gel chromatography (2.5 to 10% MeOH in CH_2Cl_2) afforded 101 mg (32%) of (S)-N-[[3-[3-fluoro-4-(N-(methoxyacetamide) piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide as a beige foam. ^1H NMR (CDCl_3) δ 7.48 (dd, $J \approx 12.9$ and 2.5 Hz, 1H); 7.10 (m, 1H); 7.00 (t, $J = 8.8$ Hz, 1H); 6.00 (brt, 1H); 4.77 (m, 1H); 4.46 (m, 1H); 4.13 (s, 2H); 4.03 (t, $J = 8.9$ Hz, 1H); 3.5-3.8 (m, 6H); 3.44 (s, 3H); 3.43 (m, 1H); 2.03 (s, 3H); and 1.7-1.9 (m, 2H).

Example 6

25 (S)-N-[[3-[3-Fluoro-4-(N-(methanesulfonamide)piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide



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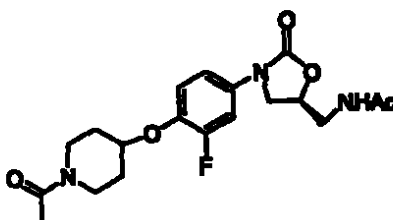
152 5/1

Compound 8

To a solution of 115 mg (0.33 mmol) of Compound 2 in 5 mL CH_2Cl_2 was added 0.05 mL (0.36 mmol) NEt_3 and 0.03 mL (0.39 mmol) methanesulfonyl chloride. The reaction stirred at rt for 22 h, was poured into 50 mL H_2O , and extracted with CH_2Cl_2 . The combined organic layers were washed with H_2O , dried over MgSO_4 , filtered, and the solvent removed by rotary evaporation to yield the impure sulfonamide. The sulfonamide was purified by dissolving in EtOAc, washing with sat. NaHCO_3 , drying over MgSO_4 , and removal of the solvent under reduced pressure to give (S)-N-[[3-[3-fluoro-4-(N-(methanesulfonamide)piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl] acetamide; mp 123-125°C, MS (CI) $[M+H]^+$ 430.

Example 7

(S)-N-[[3-[3-Fluoro-4-(N-(acetyl)piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide



Compound 7

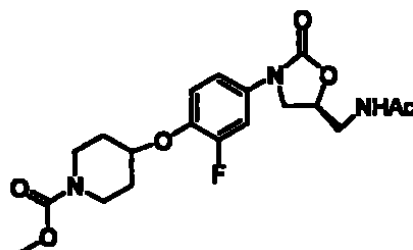
To a solution of 155 mg (0.44 mmol) of Compound 2 in 30 mL CH_2Cl_2 was added 0.10 mL (0.72 mmol) NEt_3 and 0.05 mL (0.70 mmol) acetyl chloride. The reaction stirred at rt for 18 h, was poured into 50 mL H_2O , and extracted with CH_2Cl_2 . The combined organic layers were washed with H_2O , dried over MgSO_4 , filtered, and the solvent removed by rotary evaporation to yield the impure amide. The amide was purified by dissolving in EtOAc, washing with sat. NaHCO_3 , drying over MgSO_4 , and the solvent removed under reduced pressure to give (S)-N-[[3-[3-fluoro-4-(N-(acetyl)piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide. ^1H NMR (CDCl_3) δ 7.47 (dd, J = 12.9 and 2.2 Hz, 1H); 7.06 (m, 2H); 6.97 (brt, J = 8.8 Hz, 1H); 4.79

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(m, 1H); 4.46 (m, 1H); 4.03 (t, $J = 9.0$ Hz, 1H); 3.6-3.8 (m, 6H); 3.52 (m, 1H); 2.12 (s, 3H); 2.02 (s, 3H); and 1.88 (m, 4H).

Example 8

5 (S)-N-[[3-[3-Fluoro-4-[N-(methylester)piperidinyl-4-oxy]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide



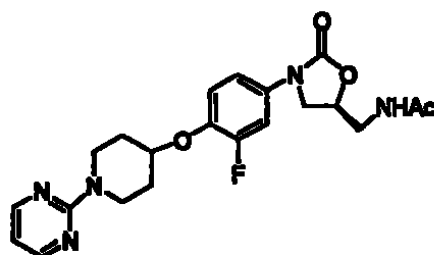
Compound 8

10 To a solution of 201 mg (0.57 mmol) of Compound 2 in 50 mL EtOAc was added 0.15 mL NEt_3 and 0.10 mL methylchloroformate. The reaction stirred at rt for 20 h, was poured into 50 mL H_2O , and extracted with EtOAc. The combined organic layers were washed with H_2O , dried over MgSO_4 , filtered, and the solvent removed by rotary evaporation to yield 167 mg (72%)
15 of (S)-N-[[3-[3-fluoro-4-[N-(methylester)piperidinyl-4-oxy]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide as a white solid. ^1H NMR (CDCl_3) δ 7.47 (m, 1H); 7.26 (m, 1H); 7.06 (m, 1H); 6.03 (m, 1H); 4.78 (m, 1H); 4.41 (m, 1H); 4.02 (t, $J = 8.9$ Hz, 1H); 3.71 (s, 3H); 3.6-3.7 (m, 5H); 3.41 (m, 2H); 2.02 (s, 3H); 1.89 (m, 2H); and 1.79 (m, 2H).

20

Example 9

(S)-N-[[3-[3-Fluoro-4-[N-(2-pyrimidinyl)piperidinyl-4-oxy]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide



25

Compound 9

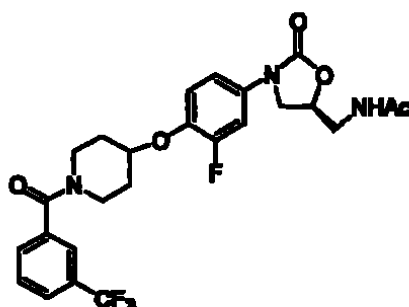
154 ~~15~~

To a solution of 176 mg (0.50 mmol) of Compound 2 in 7.5 mL EtOH was added 0.23 mL NEt₃ and 61 mg (0.53 mmol) 2-chloropyrimidine and the reaction heated at reflux for 21 h. After cooling, the reaction was poured into 50 mL sat. NaHCO₃ and extracted with CH₂Cl₂ (4 x 50 mL). The combined organic layers were washed with H₂O, dried over MgSO₄, filtered, and the solvent removed by rotary evaporation to yield 174 mg (81%) of (S)-N-[[3-[3-fluoro-4-(N-(2-pyrimidinyl)piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide; mp 121-123°C, MS (CI) [M+H]⁺ 430.

10

Example 10

(S)-N-[[3-[3-Fluoro-4-(N-(3-trifluoromethylbenzoyl)piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide



15

Compound 10

To a solution of 101 mg (0.29 mmol) of Compound 2 in 10 mL CH₂Cl₂ was added 260 mg AMBERLYST 21 Basic Resin and 1.0 mL (6.6 mmol) 3-trifluoromethylbenzoyl chloride and the reaction shaken for 3.5 h at rt. Then 2.4 g P-trisamine was added and the reaction shaken overnight. The reaction was filtered and the resin washed with CH₂Cl₂. The combined organic layers were washed with sat. NaHCO₃, dried over MgSO₄, filtered, and the solvent removed by rotary evaporation to yield the crude amide. The amide was triturated with hexanes 3 times to afford 100 mg (67%) of (S)-N-[[3-[3-fluoro-4-(N-(3-trifluoromethylbenzoyl)piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl] acetamide as a white powder; mp 150-152°C, MS (CI) [M+H]⁺ 524.

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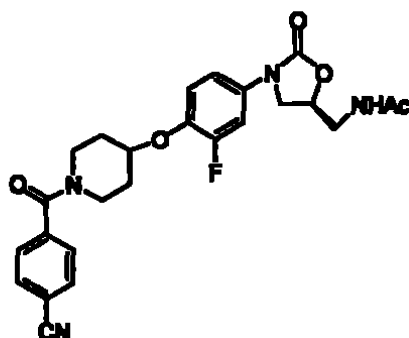
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Example 11

(S)-N-[[3-[3-Fluoro-4-[N-(4-cyanobenzoyl)piperidin-4-oxyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

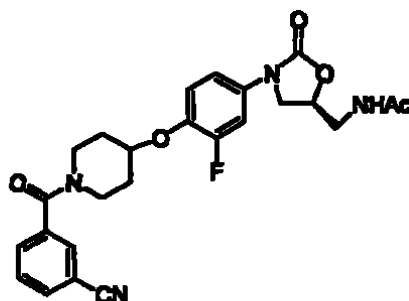


Compound 11

To a solution of 51 mg (0.15 mmol) of Compound 2 in 7.5 mL CH_2Cl_2 was added 207 mg AMBERLYST 21 Basic Resin and 116 mg (0.70 mmol) 4-cyanobenzoyl chloride and the reaction was shaken for 18 h at rt. Then 250 mg P-trisamine was added and the reaction was shaken for 20 h. The reaction was filtered and the resin washed with CH_2Cl_2 . The organic solvent was removed by rotary evaporation to yield 63 mg (91%) of (S)-N-[[3-[3-fluoro-4-[N-(4-cyanobenzoyl)piperidin-4-oxyl]phenyl]-2-oxo-5-oxazolidinyl]methyl] acetamide; mp 75-78°C, MS (CI) $[\text{M}+\text{H}]^+$ 481.

Example 12

(S)-N-[[3-[3-Fluoro-4-[N-(3-cyanobenzoyl)piperidin-4-oxyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide



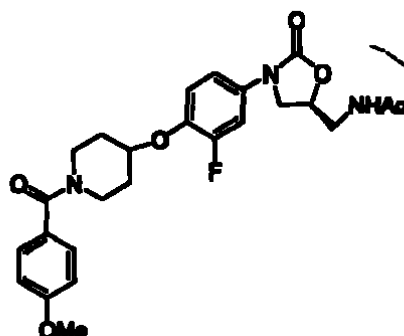
Compound 12

To a solution of 75 mg (0.21 mmol) of Compound 2 in 7.5 mL CH_2Cl_2 was added 200 mg AMBERLYST 21 Basic Resin and 128 mg (0.77 mmol) 3-

cyanobenzoyl chloride and the reaction was shaken for 18 h at rt. Then 300 mg P-trisamine was added and the reaction was shaken for 20 h. The reaction was filtered and the resin washed with CH_2Cl_2 . The organic solvent was removed by rotary evaporation to yield 103 mg (100%) of (S)-N-[[3-[3-fluoro-4-(N-(3-cyanobenzoyl)piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide; mp 82-85°C, MS (CI) $[M+H]^+$ 481.

Example 13

(S)-N-[[3-[3-Fluoro-4-(N-(4-methoxybenzoyl)piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

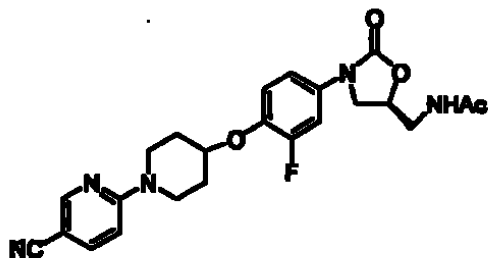


Compound 13

To a solution of 133 mg (0.29 mmol) of Compound 2 in 10 mL CH_2Cl_2 was added 350 mg AMBERLYST 21 Basic Resin and 255 mg (1.49 mmol) *p*-anisoyl chloride and the reaction was shaken for 3 h at rt. Then 1.0 g P-trisamine was added and the reaction was shaken for 48 h. The reaction was filtered and the resin washed with CH_2Cl_2 . The organic solvent was removed by rotary evaporation to yield (S)-N-[[3-[3-fluoro-4-(N-(4-methoxybenzoyl)piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide as a yellow glass; ^1H NMR (CDCl_3) δ 7.50 (m, 1H); 7.39 (m, 2H); 7.05 (m, 1H); 7.03 (m, 1H); 6.90 (m, 2H); 6.02 (m, 1H); 4.78 (m, 1H); 4.55 (m, 1H); 4.01 (m, 1H); 3.90 (s, 3H); 3.6-3.9 (m, 7H); 2.06 (s, 3H); and 1.95 (m, 4H).

Example 14

(S)-N-[[3-[3-Fluoro-4-(N-(5-cyano-2-pyridyl)piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

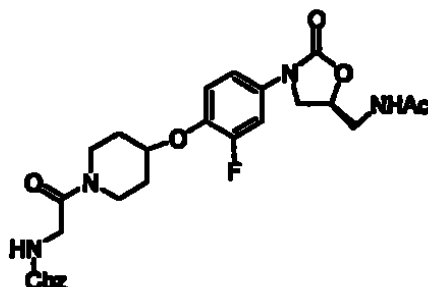


Compound 14

To a solution of 170 mg (0.48 mmol) of Compound 2 in 15 mL EtOH was added 0.15 mL NEt₃ and 80 mg (0.58 mmol) 2-chloropyridine-5-carbonitrile and the reaction was heated at 80°C for 72 h. After cooling, the reaction was poured into 50 mL H₂O and extracted with CH₂Cl₂. The combined organic layers were dried over MgSO₄, filtered, and the solvent removed by rotary evaporation to yield the crude product. Silica gel chromatography (1% MeOH in EtOAc) yielded 160 mg (73%) of (S)-N-[[3-[3-fluoro-4-{N-(5-cyano-2-pyridyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide as a yellow solid; mp 78-84°C, MS (CI) [M+H]⁺ 454.

Example 15

(S)-N-[[3-[3-Fluoro-4-{N-(α-phenylmethoxycarbonylaminoacetamide)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide



Compound 15

To a solution of 266 mg (0.76 mmol) of Compound 2 in 15 mL CH₂Cl₂ was added 0.2 mL NEt₃ and 188 mg (0.89 mmol) phenylmethoxycarbonylglycine acid fluoride and the reaction was stirred at rt

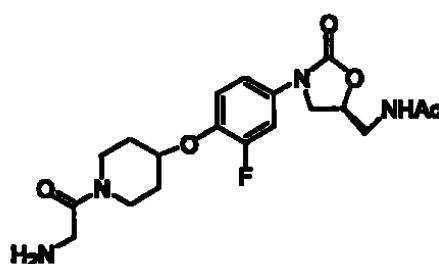
158 27

for 1.5 h. Then the reaction was poured into 50 mL sat. NaHCO_3 and extracted with CH_2Cl_2 . The combined organic layers were dried over MgSO_4 , filtered, and the solvent removed by rotary evaporation afford 375 mg (91%) of crude (S)-N-[[3-[3-fluoro-4-(N-(α -phenylmethoxycarbonylamino acetamide)piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide. ^1H NMR (CDCl_3) δ 7.50 (m, 1H); 7.39 (m, 5H); 7.11 (m, 1H); 7.03 (m, 1H); 6.24 (m, 1H); 5.87 (m, 1H); 5.15 (s, 2H); 4.75 (m, 1H); 4.52 (m, 1H); 4.06 (m, 3H); 3.6-3.8 (m, 6H); 3.37 (m, 1H); 2.10 (s, 3H); and 1.90 (m, 4H).

10

Example 16

(S)-N-[[3-[3-Fluoro-4-(N- α -aminoacetamide)piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide



Compound 16

15

A solution of 340 mg (0.62 mmol) of Compound 15 in 30 mL of EtOH was treated with 36 mg 10% Pd/C, followed by hydrogenation at 50 psi overnight. The suspension was filtered through celite and the filtrate evaporated under reduced pressure to afford crude amine. Tritration of the crude solid with CHCl_3 yielded (S)-N-[[3-[3-fluoro-4-(N- α -amino acetamide)piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl] acetamide; mp 142-146°C, MS (CI) $[\text{M}+\text{H}]^+$ 409.

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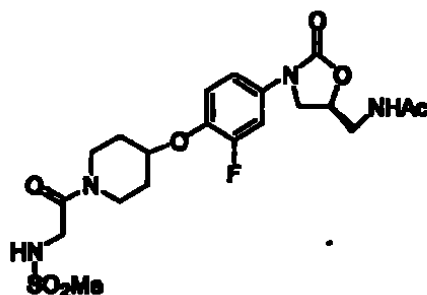
Example 17

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(S)-N-[[3-[3-Fluoro-4-(N-(sulfonamidedeglycine)piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

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Compound 17

(S)-N-[[3-[3-Fluoro-4-(N-(glycyl)pyrrolidin-4-yl)oxy]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide:

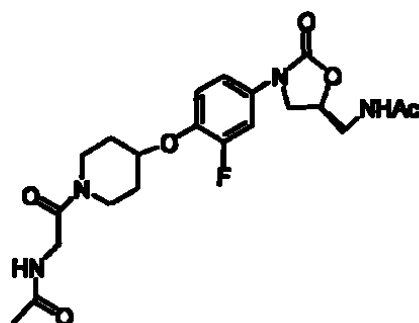
To a solution of 750 mg (4.28 mmol) Boc-glycine in 25 mL CH₂Cl₂ was added 0.8 mL DAST and the reaction stirred at rt for 20 min. Then the reaction was washed with cold H₂O, the organic layer dried over MgSO₄, filtered, and the solvent removed under reduced pressure to give a brown solid. To a solution of this acid fluoride in 40 mL CH₂Cl₂ was added 327 mg (0.70 mmol) of the TFA salt from Example 2 and 0.23 mL NEt₃ and the reaction stirred at rt for 16 h. The reaction was poured into 50 mL sat. NaHCO₃, extracted with CH₂Cl₂, washed with H₂O, dried over MgSO₄, filtered, and the solvent removed under reduced pressure to give 388 mg of the amide as a beige foam. To a solution of 0.70 mmol of this amide was added 0.55 mL trifluoroacetic acid and the reaction stirred at rt for 20 h. The volatiles were evaporated under reduced pressure to give a brown oil. To this TFA salt in 30 mL CH₂Cl₂ was added 0.23 mL NEt₃ and 0.07 mL (0.90 mmol) methanesulfonyl chloride and the reaction stirred at rt for 18 h. The reaction was poured into 50 mL sat. NaHCO₃, extracted with CH₂Cl₂, washed with H₂O, dried over MgSO₄, filtered, and the solvent removed under reduced pressure to give the crude sulfonamide. Purification by silica gel chromatography (5% MeOH in CH₂Cl₂) yielded 109 mg (32%) of (S)-N-[[3-[3-fluoro-4-(N-(sulfonamidoglycine)pyrrolidin-4-yl)oxy]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide as a white foam; mp 78-82°C, MS (CI) [M+H]⁺ 487.

Example 18

(S)-N-[[3-[3-Fluoro-4-(N-(acetyl)glycine)pyrrolidin-4-yl]oxy]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

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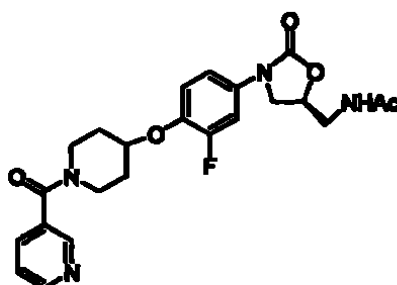


Compound 18

To a solution of 74 mg (0.63 mmol) acetylglycine in 10 mL CH_2Cl_2 was added 125 mg (0.65 mmol) EDCI and the reaction stirred at rt for 2 h. Then a solution of 304 mg (0.65 mmol) TFA salt from Example 2 and 0.15 mL (1.07 mmol) NEt_3 in 10 mL CH_2Cl_2 was added and the reaction stirred at rt for 3 h. The reaction was poured into 10 mL H_2O and extracted with CH_2Cl_2 . The combined organic layers were dried over MgSO_4 , filtered, and the solvent removed by rotary evaporation to yield the crude product as a yellow oil. Silica gel chromatography (5% MeOH in CH_2Cl_2) yielded 161 mg of (S)-N-[[3-fluoro-4-{N-(acetylglycine)piperidin-4-yl}oxy]phenyl]-2-oxo-5-oxazolidinylmethyl] acetamide; mp 66-68°C, MS (CI) $[\text{M}+\text{H}]^+$ 451.

Example 19

(S)-N-[[3-[3-Fluoro-4-{N-(3-pyridoyl)piperidin-4-yl}oxy]phenyl]-2-oxo-5-oxazolidinylmethyl]acetamide



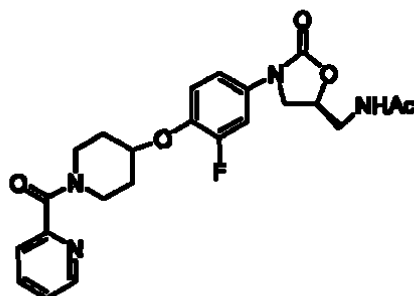
Compound 19

To a solution of 257 mg (0.55 mmol) of the TFA salt in Example 2 in 20 mL CH_2Cl_2 was added 0.4 mL (2.86 mmol) NEt_3 and 105 mg (0.59 mmol) nicotinoyl chloride hydrochloride and the reaction stirred at rt for 20 h. The

reaction was poured into 50 mL sat. NaHCO_3 and extracted with CH_2Cl_2 . The combined organic layers were washed with H_2O , dried over MgSO_4 , filtered, and the solvent removed by rotary evaporation to yield 181 mg (84%) of (S)-N-[[3-[3-fluoro-4-(N-(3-pyridoyl)piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide; mp 49-53°C, MS (CI) $[\text{M}+\text{H}]^+$ 457.

Example 20

(S)-N-[[3-[3-Fluoro-4-(N-(2-pyridoyl)piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide



Compound 20

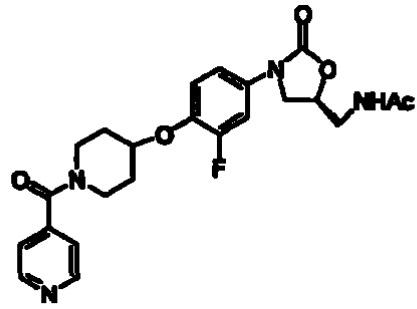
To a solution of 281 mg (0.60 mmol) of the TFA salt in Example 2 in 50 mL CH_2Cl_2 was added 0.3 mL NEt_3 and 110 mg (0.62 mmol) pyridine 2-carbonyl chloride hydrochloride and the reaction stirred at rt for 72 h. The reaction was poured into 50 mL sat. NaHCO_3 and extracted with CH_2Cl_2 . The combined organic layers were washed with H_2O , dried over MgSO_4 , filtered, and the solvent removed by rotary evaporation to yield 190 mg (69%) of (S)-N-[[3-[3-fluoro-4-(N-(2-pyridoyl)piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide; mp 55-58°C, MS (CI) $[\text{M}+\text{H}]^+$ 457.

Example 21

(S)-N-[[3-[3-Fluoro-4-(N-(4-pyridoyl)piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

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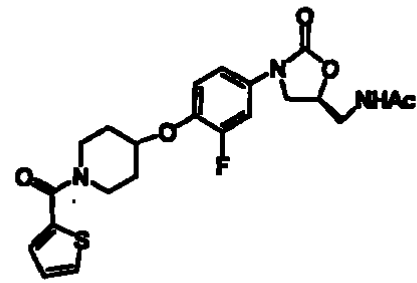


Compound 21

To a solution of 285 mg (0.61 mmol) of the TFA salt in Example 2 in 25 mL CH_2Cl_2 was added 0.5 mL NEt_3 and 123 mg (0.69 mmol) isonicotinoyl chloride hydrochloride and the reaction stirred at rt for 20 h. The reaction was poured into 50 mL sat. NaHCO_3 , and extracted with CH_2Cl_2 . The combined organic layers were washed with H_2O , dried over MgSO_4 , filtered, and the solvent removed by rotary evaporation to yield 29 mg (10%) of (S)-N-[[3-[3-fluoro-4-[N-(4-pyridyl)piperidinyl-4-oxy]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide as a white foam. ^1H NMR (CDCl_3) δ 8.73 (m, 2H); 7.50 (m, 1H); 7.41 (m, 2H); 7.06 (m, 2H); 6.06 (br t, 1H); 4.89 (m, 1H); 4.54 (m, 1H); 4.04 (m, 1H); 3.90 (m, 2H); 3.6-3.8 (m, 4H); 3.34 (m, 1H); 2.03 (s, 3H); 1.97 (m, 2H); and 1.82 (m, 2H).

Example 22

(S)-N-[[3-[3-Fluoro-4-[N-(2-thiophenecarbonyl)piperidinyl-4-oxy]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide



Compound 22

To a solution of 251 mg (0.55 mmol) of the TFA salt in Example 2 in 25 mL CH_2Cl_2 was added 0.2 mL NEt_3 and 0.07 mL (0.65 mmol) 2-

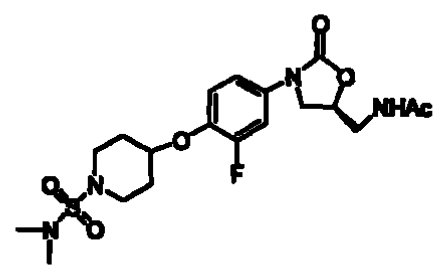
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thiophenecarbonyl chloride and the reaction stirred at rt for 72 h. The reaction was poured into 50 mL sat. NaHCO₃ and extracted with CH₂Cl₂. The combined organic layers were washed with H₂O, dried over MgSO₄, filtered, and the solvent removed by rotary evaporation to give the crude product. The crude material was dissolved in 50 mL CH₂Cl₂, P-trisamine resin added and the mixture stirred for 2 h. The reaction was filtered and the solvent evaporated under reduced pressure to give (S)-N-[[3-[3-fluoro-4-(N-(2-thiophenylcarbonyl)piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide; mp 48-51°C, MS (CI) [M+H]⁺ 462.

Example 23

(S)-N-[[3-[3-Fluoro-4-(N-(dimethylsulfamoyl)piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide



Compound 23

To a solution of 179 mg (0.38 mmol) of the TFA salt in Example 2 in 20 mL CH₂Cl₂ was added 0.12 mL NEt₃ and 0.05 mL (0.47 mmol) dimethylsulfamoyl chloride and the reaction stirred at rt for 18 h. The reaction was poured into 50 mL sat. NaHCO₃ and extracted with CH₂Cl₂. The combined organic layers were washed with H₂O, dried over MgSO₄, filtered, and the solvent removed by rotary evaporation to give the crude product. The crude oil was crystallized from warm CH₂Cl₂/Et₂O to give (S)-N-[[3-[3-fluoro-4-(N-(dimethylsulfamoyl)piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide as a white solid; mp 132-134°C, MS (CI) [M+H]⁺ 459.

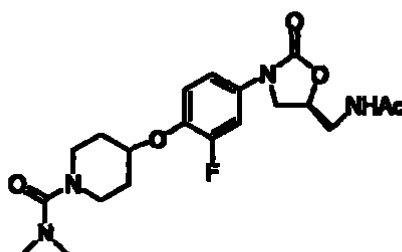
Example 24

(S)-N-[[3-[3-Fluoro-4-(N-(dimethylcarbonyl)piperidinyl-4-oxy)phenyl]-

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2-oxo-5-oxazolidinyl[methyl]acetamide

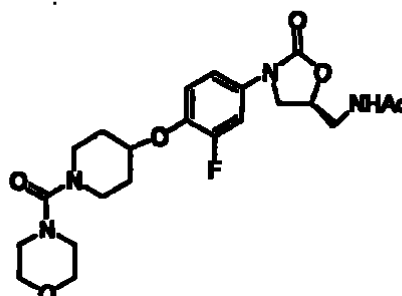


Compound 24

To a solution of 229 mg (0.49 mmol) of the TFA salt in Example 2 in 20 mL CH_2Cl_2 was added 0.15 mL (1.08 mmol) NEt_3 and 0.06 mL (0.65 mmol) dimethylcarbamoylchloride and the reaction stirred at rt overnight. The reaction was poured into 50 mL sat. NaHCO_3 and extracted with CH_2Cl_2 . The combined organic layers were washed with H_2O , dried over MgSO_4 , filtered, and the solvent removed by rotary evaporation to give the crude product. The crude oil was crystallized from warm $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$ to give 175 mg (85%) of (S)-N-[[3-[3-fluoro-4-(N-(dimethylcarbamoyl)piperidin-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide as a white solid; mp 129-131°C, MS (CI) $[\text{M}+\text{H}]^+$ 423.

Example 25

(S)-N-[[3-[3-Fluoro-4-(N-(4-morpholinecarbonyl)piperidin-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide



Compound 25

To a solution of 205 mg (0.44 mmol) of the TFA salt in Example 2 in 25 mL CH_2Cl_2 was added 0.13 mL NEt_3 and 0.06 mL (0.51 mmol) 4-morpholinecarbonyl chloride and the reaction stirred for 4 h. The reaction was poured into 50 mL sat. NaHCO_3 and extracted with CH_2Cl_2 . The

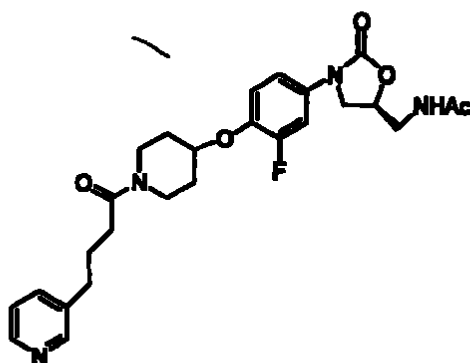
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combined organic layers were washed with H₂O, dried over MgSO₄, filtered, and the solvent removed by rotary evaporation to give the crude product. The crude product was triturated with Et₂O and hexanes to give 198 mg (97%) of (S)-N-[[3-[3-fluoro-4-(N-(4-morpholinecarbonyl)piperidin-4-yl)oxy]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide as a white solid; mp 167-170°C, MS (CI) [M+H]⁺ 485.

Example 26

(S)-N-[[3-[3-Fluoro-4-(N-(4-pyridin-3-yl-butyl)piperidin-4-yl)oxy]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide



Compound 26

4-Pyridin-3-yl-butylonitrile:

To a solution of 0.88 mL (5.11 mmol) 3-pyridine propanol in 5 mL CH₂Cl₂ at 0°C was added 0.82 mL (7.87 mmol) pyridine and 0.47 mL (6.14 mmol) methanesulfonyl chloride and the reaction stirred for 4 h. The solution was concentrated under reduced pressure and the crude mesylate dissolved in 10 mL DMF. To this solution was added 902 mg (18.41 mmol) sodium cyanide and the reaction stirred at 60°C for 3 days. Then the solution was cooled, diluted with H₂O (30 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with H₂O, dried over MgSO₄, and the solvent removed under reduced pressure to give a dark red oil. The crude nitrile was purified by dissolving in EtOAc, washing with H₂O, concentrating, and filtering through a silica gel plug (5% MeOH in CH₂Cl₂) to yield 425 mg (57%) of the nitrile.

166 167

4-Pyridin-3-yl-butyric acid:

A solution of 425 mg (2.91 mmol) of 4-pyridin-3-yl-butyronitrile in 15 mL conc. HCl was refluxed for 8 h. The volatiles were evaporated under reduced pressure and the residue dissolved in EtOH. Upon addition of acetone and cooling a dark brown solid precipitated. The filtrate was concentrated and triturated with cold acetone to collect a total of 334 mg (69%) of the carboxylic acid.

4-Pyridin-3-yl-butyryl chloride:

To a solution of 247 mg (1.49 mmol) of 4-pyridin-3-yl-butyric acid in 10 mL CH₂Cl₂ was added one drop DMF and 2.3 mL (4.56 mmol) oxalyl chloride and the mixture stirred at rt for 4 h. The volatiles were evaporated under reduced pressure and the material used crude in the following procedure.

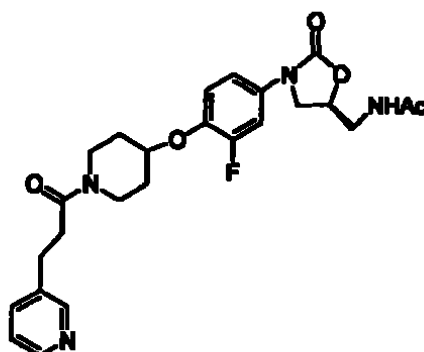
(S)-N-[[3-[3-fluoro-4-(N-(4-pyridin-3-yl-butyryl) piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (Compound 26):

To a solution of 567 mg (1.29 mmol) of the TFA salt in Example 2 in 20 mL CH₂Cl₂ was added 0.54 mL (3.86 mmol) NEt₃ at 0°C and the reaction stirred for 30 min, warming to rt. Then the solution was cooled to 0°C, a solution of the previous acid chloride in 20 mL CH₂Cl₂ was added, and the reaction allowed to warm to rt. The reaction was diluted with CH₂Cl₂, washed with sat. NaHCO₃ (2 x 30 mL), washed with H₂O (2 x 30 mL), dried over MgSO₄, filtered, and the solvent removed by rotary evaporation to give the crude product as a tan foam. Purification by silica gel chromatography (10% MeOH in EtOAc) yielded 152 mg (24%) of (S)-N-[[3-[3-fluoro-4-(N-(4-pyridin-3-yl-butyryl) piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide as an off-white foam; mp 42-45°C, MS (CI) [M+H]⁺ 499.

Example 27

(S)-N-[[3-[3-Fluoro-4-(N-(3-pyridin-3-yl-propionyl) piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

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Compound 27

3-Pyridine propionyl chloride:

5 To a solution of 300 mg (1.99 mmol) 3-pyridine propionic acid in 10 mL CH_2Cl_2 was added one drop DMF and 2.3 mL (4.56 mmol) oxalyl chloride, and the mixture stirred at rt for 4 h. The volatiles were evaporated under reduced pressure and the material used crude in the following procedure.

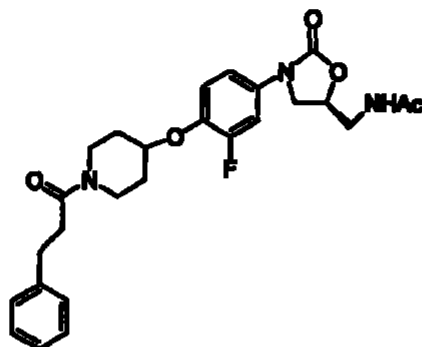
10 (S)-N-[[3-[3-fluoro-4-(N-(3-pyridin-3-yl-propionyl)piperidin-4-yl-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (Compound 27):

To a solution of 917 mg (1.97 mmol) of the TFA salt in Example 2 in 20 mL CH_2Cl_2 was added 0.75 mL (5.41 mmol) NEt_3 at 0°C and the reaction stirred for 30 min, warming to rt. Then the solution was cooled to 0°C , a solution of the previous acid chloride in 20 mL CH_2Cl_2 was added along with an additional equivalent of NEt_3 , and the reaction allowed to warm to rt and stirred overnight. The reaction was diluted with CH_2Cl_2 , washed with sat. NaHCO_3 (2 x 30 mL), washed with H_2O (2 x 30 mL), dried over Na_2SO_4 , filtered, and the solvent removed by rotary evaporation to give the crude product as a dark orange oil. Purification by silica gel chromatography (10% MeOH and 1% NEt_3 in EtOAc) yielded 110 mg of (S)-N-[[3-[3-fluoro-4-(N-(3-pyridin-3-yl-propionyl)piperidin-4-yl-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide as a foam; mp $45-47^\circ\text{C}$, MS (CI) $[\text{M}+\text{H}]^+$ 485.

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Example 28

(S)-N-[[3-[3-Fluoro-4-(N-(3-phenyl-propionyl)piperidin-4-yl-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

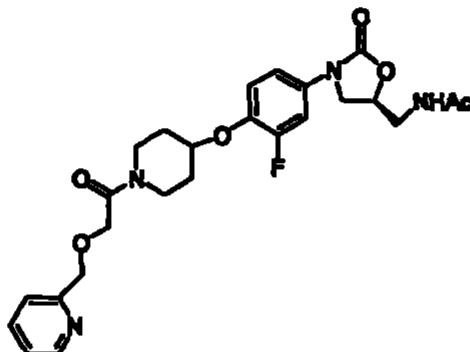


Compound 28

To a solution of 133 mg (0.27 mmol) of the TFA salt in Example 2 in 20 mL CH_2Cl_2 was added 0.07 mL (0.53 mmol) NEt_3 and 0.04 mL (0.29 mmol) hydrocinnamoyl chloride, and the reaction allowed to warm to rt and stirred for 1 h. The reaction was diluted with CH_2Cl_2 , washed with sat. NaHCO_3 (2 x 30 mL), washed with H_2O (2 x 30 mL), dried over Na_2SO_4 , filtered, and the solvent removed by rotary evaporation to give the crude product as a colorless oil. Purification by silica gel chromatography (10% MeOH in EtOAc) yielded a transparent glass. This material was triturated with EtOAc and hexanes to give (S)-N-[[3-[3-fluoro-4-{N-(3-phenyl-propionyl)pyrrolidin-4-yl}oxy]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide as a white solid; MS (CI) $[\text{M}+\text{H}]^+$ 484.

Example 29

(S)-N-[[3-[4-{N-(Pyridin-2-yloxyacetamide)pyrrolidin-4-yl}oxy]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide



Compound 29

169 170

(Pyridin-2-yl-methoxy)-acetic acid t-butyl ester:

To a solution of 0.5 mL (5.18 mmol) 2-pyridylmethanol in 20 mL THF at 0°C was added 270 mg (6.75 mmol) NaH and the reaction stirred for 0.25 h. Then 0.82 mL t-butylbromoacetate was added and the reaction warmed to rt and stirred for 12 days. The reaction was poured into 100 mL H₂O, extracted with CH₂Cl₂ (2 x 100 mL), the combined organic layers washed with brine, dried over MgSO₄, filtered, and the solvent removed under reduced pressure to give 1.16 g (61%) as a brown oil.

(Pyridin-2-yl-methoxy)-acetic acid:

To a solution of 706 mg (3.16 mmol) of (pyridin-3-yl-methoxy)-acetic acid t-butyl ester and 1.5 mL of TFA in 25 mL of methylene chloride were stirred at room temperature for 20 hr. The volatiles are evaporated to afford crude acid.

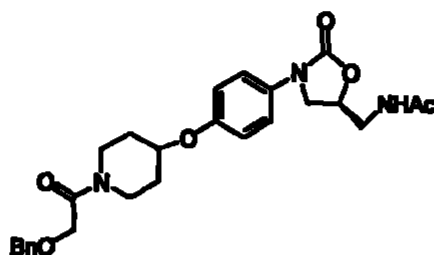
(S)-N-[[3-[4-(N-(Pyridin-2-yloxyacetamide)piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (Compound 29):

To 460 mg (1.63 mmol) of (pyridin-2-yl-methoxy)acetic acid in 100 mL CH₂Cl₂ was added 405 mg (2.11 mmol) EDCI, 634 mg (1.36 mmol) of the TFA salt from example 1, and 4.5 mL (32.2 mmol) NEt₃. The reaction was stirred at rt for 5 days. Then the mixture was poured into 125 mL H₂O, extracted with CH₂Cl₂, the organic layers washed with brine, dried over MgSO₄, filtered, and the solvent removed by rotary evaporation. Purification by silica gel chromatography (5% MeOH in CH₂Cl₂) yielded 403 mg (56%) of (S)-N-[[3-[4-(N-(pyridin-2-yloxyacetamide)piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide as a yellow semi-solid. ¹H NMR (CDCl₃) δ 8.54 (m, 1H); 7.72 (m, 1H); 7.49 (m, 2H); 7.23 (m, 1H); 7.09 (m, 1H); 7.00 (m, 1H); 6.10 (m, 1H); 4.78 (m, 1H); 4.71 (s, 2H); 4.48 (m, 1H); 4.32 (s, 2H); 4.04 (m, 1H); 3.6-3.8 (m, 6H); 3.45 (m, 1H); 2.03 (s, 3H); and 1.83 (m, 4H).

Example 30

(S)-N-[[3-[4-(N-(Benzyloxyacetamide)piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

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Compound 30

1-[N-(t-Butoxycarbonyl)piperidin-4-yl]-4-oxy-4-nitrobenzene:

- 5 To a solution of 10.0 g (49.68 mmol) of N-(t-butoxycarbonyl)-4-piperidinol from example 1 in 125 mL dry THF at 0°C was added dropwise 74 mL (74.53 mmol) 1M KOtBu. After stirring at 0°C for 0.5 h, 5.27 mL (49.68 mmol) p-fluoronitrobenzene was added and the reaction warmed to rt and stirred overnight. The volatiles were removed under reduced pressure and
- 10 the reaction diluted with 800 mL H₂O. The mixture was extracted with CH₂Cl₂ (2 x 500 mL) and a brown solid removed by filtration. The combined aqueous layers were washed with H₂O, dried with MgSO₄, filtered, and the solvent removed by rotary evaporation to give an orange solid. Purification by silica gel chromatography (3:1 hexane:EtOAc) yielded 6.98 g (44%) of 1-[N-(t-butoxycarbonyl)piperidin-4-yl]-4-oxy-4-nitrobenzene as a pale yellow solid. An
- 15 additional 3.20 g of product was extracted from the brown solid; MS (CI) [M+Na]⁺ 345.

1-[4-(N-(t-Butoxycarbonyl)piperidin-4-yl)-4-oxy-4-aminobenzene:

- 20 To 6.97 g (21.62 mmol) of 1-[N-(t-butoxycarbonyl)piperidin-4-yl]-4-nitrobenzene in 250 mL MeOH was added 6.81 g (108.1 mmol) ammonium formate and a catalytic amount of 10% Pd/C, and the reaction heated at 50°C under N₂ for 5 h. The reaction was filtered through a pad of celite and the filtrate evaporated to afford crude aniline as an orange oil. The material was
- 25 used without further purification in the next step.

4-(N-(t-Butoxycarbonyl)-4-piperidinyl)-1-(phenylmethoxycarbonylamino)benzene:

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To 6.32 g (21.62 mmol) of 1-[4-(N-*t*-butoxycarbonyl)piperidinyl-4-oxy]-4-aminobenzene in 300 mL 2:1 acetone:H₂O at 0°C was added 4.50 g (52.97 mmol) NaHCO₃ and 3.30 mL (23.13 mmol) benzylchloroformate. The reaction was allowed to warm to rt and stirred overnight. Then the volatiles were evaporated, the residue diluted with 200 mL H₂O and extracted with Et₂O (2 x 200 mL). The combined organic layers were washed with H₂O, dried over MgSO₄, filtered, and the solvent removed by rotary evaporation to give 8.82 g (93%) of 4-[N-(*t*-butoxycarbonyl)-4-piperidinyl]-1-(phenylmethoxycarbonylamino)benzene as a pink solid; mp 107-108°C, MS (CI) [M+Na]⁺ 449.

(R)-[3-[4-[N-(*t*-Butoxycarbonyl)-4-piperidinyl]phenyl]-2-oxo-5-oxazolidinyl]methanol:

To 8.23 g (19.31 mmol) of 4-[N-(*t*-butoxycarbonyl)-4-piperidinyl]-1-(phenylmethoxycarbonylamino)benzene in 300 mL dry THF at -78°C was added 10.8 mL (27.03 mmol) 2.5M *n*-BuLi and the reaction stirred for 1 h. Then 3.84 mL (27.03 mmol) (R)-glycidyl butyrate was added via syringe and the reaction warmed to rt and stirred for 3 days. Then an additional 2 mL 2.5M *n*-BuLi was added and the reaction stirred for another day. The reaction was carefully poured into 150 mL sat. NH₄Cl (aq.) and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with H₂O, dried over MgSO₄, filtered, and the solvent removed by rotary evaporation. Silica gel chromatography (EtOAc) gave 4.34 g (57%) of (R)-[3-[4-[N-(*t*-butoxycarbonyl)-4-piperidinyl]phenyl]-2-oxo-5-oxazolidinyl]methanol as a yellow solid; mp 110-112°C, MS (CI) [M+Na]⁺ 415.

(R)-[3-[4-[N-(*t*-Butoxycarbonyl)-4-piperidinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl methanesulfonate:

To 4.23 g (10.79 mmol) of (R)-[3-[4-[N-(*t*-butoxycarbonyl)-4-piperidinyl]phenyl]-2-oxo-5-oxazolidinyl]methanol in 75 mL CH₂Cl₂ at 0°C was added 3.0 mL (21.58 mmol) NEt₃ and 1.2 mL (15.11 mmol) methanesulfonyl chloride. The reaction was allowed to warm to rt over an hour and washed with H₂O (2 x 50 mL), dried over MgSO₄, filtered, and the solvent removed by

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rotary evaporation to yield 5.0 g (99%) of (S)-[3-[4-(N-(t-butoxycarbonyl)-4-piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl methanesulfonate as a white foam.

5 (R)-[3-[4-(N-(t-Butoxycarbonyl)-4-piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methylazide:

To a solution of 5.0 g (10.63 mmol) of (R)-[3-[4-(N-(t-butoxycarbonyl)-4-piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl methanesulfonate in 100 mL DMF was added 2.63 g (40.38 mmol) sodium azide and the reaction was
10 heated at 70°C overnight. Then the reaction was poured into 200 mL H₂O and extracted with EtOAc (3 x 150 mL). The combined organic layers were washed with H₂O (2 x 150 mL), dried over MgSO₄, filtered, and the solvent removed by rotary evaporation to yield 4.4 g (99%) of (R)-[3-[4-(N-(t-butoxycarbonyl)-4-piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methylazide as a
15 yellow oil; MS (CI) [M+Na]⁺ 440.

(S)-N-[3-[4-(N-(t-Butoxycarbonyl)-4-piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methylacetamide:

A solution of 4.48 g (10.73 mmol) of (R)-[3-[4-(N-(t-Butoxycarbonyl)-4-piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methylazide in 30 mL of EtOAc was
20 treated with a catalytic amount of 10% Pd/C, followed by hydrogenation at 50 psi for 20 h. To this mixture at 0°C was added 1.1 mL (12.88 mmol) pyridine and 3.2 mL (34.34 mmol) acetic anhydride. The reaction was stirred for 30 min at 0°C, then warmed to rt over 1 h. The reaction was filtered through
25 celite, eluting with EtOAc. The volatiles were removed under reduced pressure and the yellow solid dissolved in EtOAc and washed with H₂O (3 x 100 mL). A white solid was removed via filtration. The organic layers were concentrated to an orange oil and triturated using EtOAc and hexanes to yield a white solid. The white solids were combined to yield 1.48 g (31%) of (S)-N-
30 [[3-[4-(N-(t-butoxycarbonyl)-4-piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide; mp 185-186°C, MS (CI) [M+Na]⁺ 456.

(S)-N-[3-[4-(Piperidinyl-4-oxo)phenyl]-2-oxo-5-oxazolidinyl]methylacetamide:

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CC(=O)NCC1OC(=O)N1c2ccc(Oc3ccccc3N(C(=O)O)CC4CCCCC4)cc2

Compound 31

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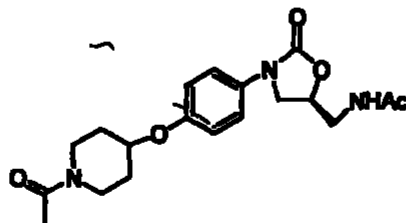
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10% Pd/C, and the reaction was heated at 50°C for 3 days. Then the reaction was filtered through a pad of celite, eluted with EtOAc and MeOH, and the solvent removed under reduced pressure to yield 58 mg (66%) of (S)-N-[[3-[4-(N-(α -hydroxyacetamide)piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide as a white foam; MS (CI) [M+H]⁺ 392.

Example 32

(S)-N-[[3-[4-(N-(Acetyl)piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide



Compound 32

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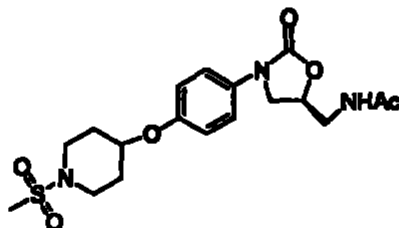
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To a solution of 240 mg (0.72 mmol) of (S)-N-[[3-[4-(piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide in 20 mL CH₂Cl₂ was added 0.45 mL (3.24 mmol) NEt₃ and 0.08 mL (1.08 mmol) acetyl chloride and the reaction stirred overnight. The reaction was diluted with 50 mL CH₂Cl₂, washed with H₂O, dried over MgSO₄, filtered, and the solvent removed by rotary evaporation to give the crude product as a gold oil. Purification by silica gel chromatography (10% MeOH in EtOAc) yielded 130 mg (50%) of (S)-N-[[3-[4-(N-(acetyl)piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide as a colorless oil; MS (CI) [M+Na]⁺ 398.

Example 33

(S)-N-[[3-[4-(N-(Methanesulfonamide)piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide



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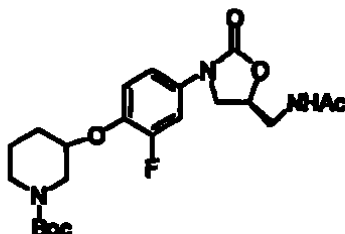
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Compound 33

To a solution of 50 mg (0.15 mmol) of (S)-N-[[3-[4-(piperidinyl-4-oxyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide in 20 mL CH₂Cl₂ was added 0.04 mL (0.30 mmol) NEt₃ and 0.02 mL (0.21 mmol) methanesulfonyl chloride and the reaction stirred overnight. The reaction was diluted with 10 mL CH₂Cl₂, washed with H₂O, dried over MgSO₄, filtered, and the solvent removed by rotary evaporation to give the crude product as a gold oil. Purification by silica gel chromatography (10% MeOH in EtOAc) yielded 40 mg (84%) of (S)-N-[[3-[4-(N-(methanesulfonamide)piperidinyl-4-oxyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide as a white solid; MS (CI) [M+Na]⁺ 434.

Example 34

(S)-N-[[3-[3-Fluoro-4-[N-(t-butoxycarbonyl)-3-piperidinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide



Compound 34

N-(t-Butoxycarbonyl)-3-piperidinol:

A solution of 10.0 g (72.67 mmol) 3-hydroxypiperidine in 100 mL dry THF at 0°C was added 10.1 mL (72.67 mmol) NEt₃ and 15.86 g (72.67 mmol) di-t-butylcarbonate in 100 mL THF and the reaction allowed to warm to rt and stirred overnight. The solvent was removed under reduced pressure, the resulting residue dissolved in 300 mL CH₂Cl₂ and the solution extracted with H₂O (2 x 200 mL), dried over MgSO₄, filtered and rotary evaporated to yield 12.66 g (87%) of N-(t-butoxycarbonyl)-3-piperidinol as an oil which slowly solidified to a white solid.

1-[N-(t-Butoxycarbonyl)piperidinyl]-3-oxyl-2-fluoro-4-nitrobenzene:

To a solution of 5.0 g (24.84 mmol) of N-(*t*-butoxycarbonyl)-3-piperidinol in 75 mL dry THF at 0°C was added dropwise 37 mL (37.26 mmol) 1M KO^tBu. After stirring at 0°C for 0.5 h, 2.8 mL (24.84 mmol) 3,4-difluoronitrobenzene was added and the reaction warmed to rt and stirred for 0.5 h. The volatiles were removed under reduced pressure and the residue was dissolved in 400 mL H₂O and extracted with CH₂Cl₂ (2 x 300 mL). The combined aqueous layers were dried with MgSO₄, filtered, and the solvent removed by rotary evaporation. Purification by silica gel chromatography (3:1 hexanes:EtOAc) yielded 5.94 g (70%) of 1-[N-(*t*-butoxycarbonyl)piperidinyl-3-oxy]-2-fluoro-4-nitrobenzene; MS (CI) [M+Na]⁺ 363.

1-[4-(N-(*t*-Butoxycarbonyl)piperidinyl-3-oxy)-2-fluoro-4-aminobenzene]

To 5.94 g (17.40 mmol) of 1-[N-(*t*-butoxycarbonyl)piperidinyl-3-oxy]-2-fluoro-4-nitrobenzene in 200 mL MeOH was added 5.49 g (87.02 mmol) ammonium formate and a catalytic amount of 10% Pd/C, and the reaction heated at 50°C under N₂ overnight. The reaction was filtered through a pad of celite and the filtrate evaporated to afford crude aniline as an orange oil. The product was dissolved in 150 mL EtOAc and washed with H₂O (2 x 100), dried over MgSO₄, filtered, and the solvent removed under reduced pressure to give 4.98 g (92%) as a light yellow oil. The material was used without further purification in the next step.

3-Fluoro-4-[N-(*t*-butoxycarbonyl)-3-piperidinyl]-1-(phenylmethoxy carbonylamino)benzene:

To 4.98 g (16.08 mmol) of 1-[4-(N-(*t*-butoxycarbonyl)piperidinyl-3-oxy)-2-fluoro-4-aminobenzene in 300 mL 2:1 acetone:H₂O at 0°C was added 3.31 g (39.40 mmol) NaHCO₃ and 2.48 mL (17.20 mmol) benzylchloroformate. After stirring at rt overnight the volatiles were evaporated, the residue diluted with 200 mL H₂O and extracted with Et₂O (3 x 150 mL). The combined organic layers were washed with H₂O, dried over MgSO₄, filtered, and the solvent removed by rotary evaporation. Silica gel chromatography (2:3 EtOAc:Hexanes) afforded 5.30 g (75%) of 3-fluoro-4-[N-(*t*-butoxycarbonyl)-3-

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piperidinyl]-1-(phenylmethoxycarbonylamino)benzene as a white solid; mp 109-110°C, MS (CI) [M+Na]⁺ 467.

(R)-[3-[3-Fluoro-4-[N-(t-butoxycarbonyl)-3-piperidinyl]phenyl]-2-oxo-5-oxazolidinyl]methanol:

- 5 To 3.27 g (7.38 mmol) of 3-fluoro-4-[N-(t-butoxycarbonyl)-3-piperidinyl]-1-(phenylmethoxy carbonylamino)benzene in 150 mL dry THF at -78°C was added 4.1 mL (10.31 mmol) 2.5M *n*-BuLi and the reaction stirred for 1 h. Then 1.5 mL (10.31mmol) (R)-glycidyl butyrate was added via syringe and the reaction warmed to rt and stirred overnight. The reaction was
10 carefully poured into 100 mL sat. NH₄Cl (aq.) and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with H₂O, dried over MgSO₄, filtered, and the solvent removed by rotary evaporation. Silica gel chromatography (EtOAc) gave 2.89 g (98%) of (R)-[3-[3-fluoro-4-[N-(t-butoxycarbonyl)-3-piperidinyl]phenyl]-2-oxo-5-oxazolidinyl]methanol as a
15 white foam; mp 48-50°C.

(R)-[3-[3-Fluoro-4-[N-(t-butoxycarbonyl)-3-piperidinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl methanesulfonate:

- 20 To 1.32 g (3.22 mmol) of (R)-[3-[3-fluoro-4-[N-(t-butoxycarbonyl)-3-piperidinyl]phenyl]-2-oxo-5-oxazolidinyl]methanol in 50 mL CH₂Cl₂ at 0°C was added 0.90 mL (6.44 mmol) NEt₃ and 0.35 mL (4.51mmol) methanesulfonyl chloride. The reaction was allowed to warm to rt over 1 h and then washed with H₂O (2 x 30 mL), dried over MgSO₄, filtered and the solvent removed by
25 rotary evaporation to yield 1.50 g (95%) of (R)-[3-[3-fluoro-4-[N-(t-butoxycarbonyl)-3-piperidinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl methanesulfonate as a yellow foam.

(R)-[3-[3-Fluoro-4-[N-(t-butoxycarbonyl)-3-piperidinyl]phenyl]-2-oxo-5-oxazolidinyl]methylazide:

- 30 To a solution of 1.50 g (3.07 mmol) of (R)-[3-[3-fluoro-4-[N-(t-butoxycarbonyl)-3-piperidinyl]phenyl]-2-oxo-5-oxazolidinyl]methyl methanesulfonate in 60 mL DMF was added 758 mg (11.66 mmol) sodium

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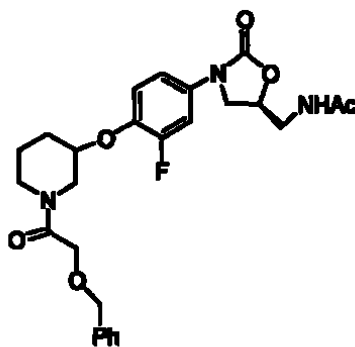
azide and the reaction heated at 75°C overnight. Then the reaction was poured into 100 mL H₂O and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with H₂O (3 x 200 mL), dried over MgSO₄, filtered, and the solvent removed by rotary evaporation to yield (R)-[3-[3-fluoro-4-(N-(t-butoxycarbonyl)-3-piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methylazide as a foam.

(S)-N-[[3-[3-Fluoro-4-(N-(t-butoxycarbonyl)-3-piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide:

A solution of 1.34 g (3.07 mmol) of (R)-[3-[3-fluoro-4-(N-(t-butoxycarbonyl)-3-piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methylazide in 30 mL of EtOAc was treated with a catalytic amount of 10% Pd/C, followed by hydrogenation at 50 psi for 20 h. To this mixture at 0°C was added 0.3 mL (3.68 mmol) pyridine and 0.93 mL (9.82 mmol) acetic anhydride. The reaction was stirred for 30 min at 0°C, then warmed to rt over 1 h. The reaction was filtered through celite, eluting with EtOAc. The volatiles were removed under reduced pressure. Silica gel chromatography (10% MeOH in EtOAc) yielded (S)-N-[[3-[4-(N-(t-butoxycarbonyl)-3-piperidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide as a white solid; mp 60-63°C, MS (CI) [M+Na]⁺ 474.

Example 35

(S)-N-[[3-[3-Fluoro-4-(N-(benzyloxyacetamide)piperidinyl-3-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide



Compound 35

(S)-N-[[3-[3-Fluoro-4-(piperidinyl-3-oxo)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide:

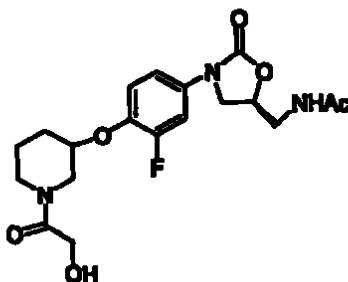
To a solution of 589 mg (1.31 mmol) of Compound 34 in 13 mL CH_2Cl_2 was added 1.0 mL (13.1 mmol) trifluoroacetic acid and the reaction stirred at
 5 rt for 2 h. The volatiles were evaporated under reduced pressure to yield (S)-N-[[3-[3-fluoro-4-(piperidinyl-3-oxo)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

10 (S)-N-[[3-[3-Fluoro-4-(N-(benzyloxyacetamide)piperidinyl-3-oxo)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide:

To a suspension of 303 mg (0.65 mmol) of (S)-N-[[3-[3-fluoro-4-(piperidinyl-3-oxo)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide in 50 mL CH_2Cl_2 was added 0.27 mL (1.96 mmol) NEt_3 and 0.11 mL (0.72 mmol) benzyloxyacetyl chloride. After stirring for 1 h, the reaction was poured into
 15 75 mL H_2O and extracted with CH_2Cl_2 (4 x 50 mL). The combined organic layers were dried over MgSO_4 , filtered, and evaporated under reduced pressure to yield (S)-N-[[3-[3-fluoro-4-(N-(benzyloxyacetamide)piperidinyl-3-oxo)phenyl]-2-oxo-5-oxazolidinyl]methyl] acetamide as a foam; MS (CI) $[M+H]^+$ 500.

20 **Example 36**

(S)-N-[[3-[3-Fluoro-4-(N-(α -hydroxyacetamide)piperidinyl-3-oxo)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide



25 **Compound 36**

To a solution of 301 mg (0.60 mmol) of Compound 35 in 10 mL MeOH was added 190 mg ammonium formate and a catalytic amount of 10% Pd/C and the reaction was heated at reflux overnight. Then the reaction was

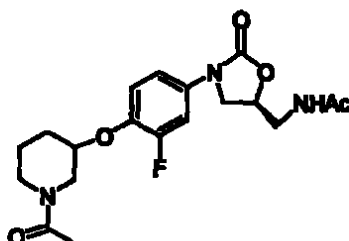
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filtered through a pad of celite and the solvent removed under reduced pressure. Silica gel chromatography (10% MeOH in EtOAc) afforded 231 mg (82%) of (S)-N-[[3-[3-fluoro-4-(N-(α -hydroxyacetamide)piperidinyl-3-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide as a yellow foam; MS (CI)

5 [M+H]⁺ 410.

Example 37

(S)-N-[[3-[3-Fluoro-4-(N-(acetyl)piperidinyl-3-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide



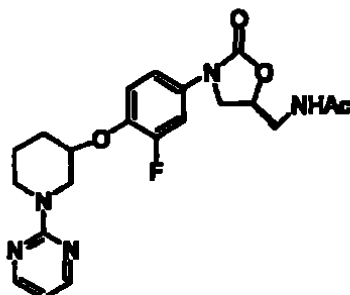
Compound 37

To a solution of 100 mg (0.28 mmol) of (S)-N-[[3-[3-fluoro-4-(piperidinyl-3-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide in 10 mL CH₂Cl₂ was added 0.12 mL (0.85 mmol) NEt₃ and 0.03 mL (0.43 mmol) acetyl chloride. The reaction stirred at rt for 2 h diluted with CH₂Cl₂, washed with H₂O (2 x 100 mL), dried over MgSO₄, filtered, and the solvent removed by rotary evaporation to yield the impure amide. Purification by silica gel chromatography (10% MeOH in EtOAc) and trituration of the resultant oil with EtOAc and hexanes yielded (S)-N-[[3-[3-fluoro-4-(N-(acetyl)piperidinyl-3-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide as a solid.

Example 38

(S)-N-[[3-[3-Fluoro-4-(N-(2-pyrimidinyl)piperidinyl-3-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

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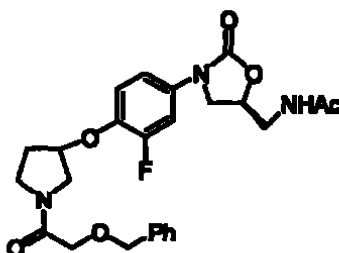


Compound 38

To a solution of 151 mg (0.33 mmol) of (S)-N-[[3-[3-fluoro-4-
5 {piperidinyl-3-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide in 4 mL
EtOH was added 0.11 mL (0.82 mmol) NEt₃ and 39 mg (0.34 mmol) 2-
chloropyrimidine and the reaction heated at reflux for 3 days. The reaction
was cooled, poured into 15 mL NaHCO₃ (sat.), extracted with CH₂Cl₂, washed
with H₂O (2 x 100 mL), dried over MgSO₄, filtered, and the solvent removed
10 by rotary evaporation to yield an orange oil. The crude oil was triturated with
EtOAc and Et₂O to give 25mg (23%) of (S)-N-[[3-[3-fluoro-4-{N-(2-
pyrimidinyl)piperidinyl-3-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide as
a pale orange solid; mp 130-131°C, MS (CI) [M+H]⁺ 429.

Example 39

(S)-N-[[3-[3-Fluoro-4-(N-(benzyloxyacetamide)pyrrolidinyl-
3-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide



Compound 39

N-(Benzyloxyacetamide)-3-pyrrolidinol:

A solution of 4.4 mL (52.93 mmol) 3-pyrrolidinol in 250 mL CH₂Cl₂ at
0°C was added 8.4 mL (60.26 mmol) NEt₃ and 8.2 mL (51.97 mmol)
benzyloxyacetyl chloride. The reaction was stirred for 3.5 h and then poured

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into 400 mL H₂O. The reaction was extracted with CH₂Cl₂, dried over MgSO₄, filtered and rotary evaporated to yield 12.0 g (98%) of N-(benzyloxyacetamide)-3-pyrrolidinol as a yellow oil.

5 1-[N-(Benzyloxyacetamide)pyrrolidinyl-3-oxy]-2-fluoro-4-nitrobenzene:

To a solution of 2.03 g (8.63 mmol) of N-(benzyloxyacetamide)-3-pyrrolidinol in 50 mL dry THF at 0°C was added dropwise 10 mL (10.0 mmol) 1M KOtBu. After stirring at 0°C for 0.5 h, 0.96 mL (8.67 mmol) 3,4-difluoronitrobenzene was added and the reaction warmed to rt and stirred overnight. The reaction was poured into 100 mL H₂O and extracted with EtOAc. The combined organic layers were washed with H₂O, dried with MgSO₄, filtered, and the solvent removed by rotary evaporation. Then the solid was recrystallized from EtOAc and hexanes to afford 2.49 g (77%) of 1-[N-(benzyloxyacetamide)pyrrolidinyl-3-oxy]-2-fluoro-4-nitrobenzene as a solid.

15 1-[4-(N-Benzyloxyacetamide)pyrrolidinyl-3-oxy]-2-fluoro-4-aminobenzene:

To 1.81 g (4.31 mmol) of 1-[N-(benzyloxyacetamide)pyrrolidinyl-3-oxy]-2-fluoro-4-nitrobenzene in 50 mL EtOH was added 4.86 g (21.5 mmol) SnCl₂ and the reaction heated at 70°C for 2 h. The reaction was poured into ice water and extracted with EtOAc and CHCl₃ (2 x 100 mL). The combined organic layers were dried over MgSO₄, filtered, and the solvent removed under reduced pressure to give 880 mg (58%) of 1-[4-(N-benzyloxyacetamide)pyrrolidinyl-3-oxy]-2-fluoro-4-aminobenzene as a yellow oil. The material was used without further purification in the next step.

25 3-Fluoro-4-[N-(benzyloxyacetamide)-3-pyrrolidinyl]-1-(phenylmethoxy carbonylamino)benzene:

To 466 mg (2.73 mmol) of 1-[4-(N-benzyloxyacetamide)pyrrolidinyl-3-oxy]-2-fluoro-4-aminobenzene in 75 mL 2:1 acetone:H₂O at 0°C was added 527 mg (8.27 mmol) NaHCO₃ and 0.88 mL (2.56 mmol) Cbz-Cl. The reaction was allowed to warm to rt and stirred overnight. The volatiles were evaporated, the residue diluted with 200 mL H₂O and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with H₂O, dried over

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MgSO₄, filtered, and the solvent removed by rotary evaporation. Silica gel chromatography (EtOAc) afforded 473 mg (38%) of 3-fluoro-4-(N-(benzyloxyacetamide)-3-pyrrolidinyl)-1-(phenylmethoxycarbonylamino); MS (CI) [M+H]⁺ 479.

5

(R)-[3-[3-Fluoro-4-(N-(benzyloxyacetamide)-3-pyrrolidinyl)phenyl]-2-oxo-5-oxazolidinyl]methanol:

To 473 mg (0.99 mmol) of 3-fluoro-4-(N-(benzyloxyacetamide)-3-pyrrolidinyl)-1-(phenylmethoxycarbonylamino)benzene in 25 mL dry THF at -78°C was added 0.55 mL (1.38 mmol) 2.5M *n*-BuLi and the reaction warmed to rt and stirred for 1 h. Then the solution was again cooled to -78°C and 0.19 mL (1.38 mmol) (R)-glycidyl butyrate was added via syringe and the reaction warmed to rt and stirred overnight. The reaction was carefully poured into 50 mL sat. NH₄Cl (aq.) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with H₂O, dried over MgSO₄, filtered, and the solvent removed by rotary evaporation. Silica gel chromatography (0% to 10% MeOH in EtOAc) gave 107 mg (25%) of (R)-[3-[3-Fluoro-4-(N-(benzyloxyacetamide)-3-pyrrolidinyl)phenyl]-2-oxo-5-oxazolidinyl]methanol as a gold oil; MS (CI) [M+Na]⁺ 445.

20

(R)-[3-[3-Fluoro-4-(N-(benzyloxyacetamide)-3-pyrrolidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl methanesulfonate:

To 107 mg (0.24 mmol) of (R)-[3-[3-fluoro-4-(N-(benzyloxyacetamide)-3-pyrrolidinyl)phenyl]-2-oxo-5-oxazolidinyl]methanol in 50 mL CH₂Cl₂ at 0°C was added 0.07 mL (0.48 mmol) NEt₃ and 0.03 mL (0.34 mmol) methanesulfonyl chloride. After warming to rt and stirring for 1 h the reaction was diluted with 10 mL CH₂Cl₂, washed with H₂O, dried over MgSO₄, filtered and the solvent removed by rotary evaporation to yield (R)-[3-[3-fluoro-4-(N-(benzyloxyacetamide)-3-pyrrolidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl methanesulfonate; MS (CI) [M+H]⁺ 523.

30

(R)-[3-[3-Fluoro-4-(N-(benzyloxyacetamide)-3-pyrrolidinyl)phenyl]-2-oxo-5-oxazolidinyl]methylazide:

To a solution of 2.22 g (4.25 mmol) of (R)-[3-[3-fluoro-4-(N-(benzyloxyacetamide)-3-pyrrolidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl methanesulfonate in 40 mL DMF was added 1.05 g (16.13 mmol) sodium azide and the reaction heated at 75°C overnight. Then the reaction was poured into 20 mL H₂O and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with H₂O, dried over Na₂SO₄, filtered, and the solvent removed by rotary evaporation to yield 1.29 g (85%) of (R)-[3-[3-Fluoro-4-(N-(benzyloxyacetamide)-3-pyrrolidinyl)phenyl]-2-oxo-5-oxazolidinyl]methylazide; MS (CI) [M+H]⁺ 471.

(S)-N-[[3-[3-Fluoro-4-(N-(benzyloxyacetamide)-3-pyrrolidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (Compound 39):

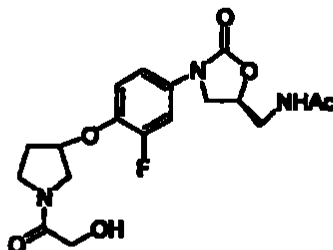
To a solution of 1.29 g (2.74 mmol) of (R)-[3-[3-fluoro-4-(N-(benzyloxyacetamide)-3-pyrrolidinyl)phenyl]-2-oxo-5-oxazolidinyl]methylazide in 30 mL MeOH was added 1.38 mL (13.71 mmol) 1,3-propanedithiol and 1.91 mL (13.71 mmol) NEt₃ and the reaction stirred overnight at rt. Then 0.78 mL (8.23 mmol) acetic anhydride and 1.33 mL (16.45 mmol) pyridine were added and the reaction stirred at rt for 3 h. The reaction was filtered through a fritted funnel, rinsed with MeOH, and concentrated under reduced pressure. Then the residue was diluted with EtOAc, washed with H₂O (3 x 100 mL), washed with brine, dried over Na₂SO₄, and the solvent removed under reduced pressure to give an orange oil. Purification by silica gel chromatography (10% MeOH in EtOAc) gave 1.02 g (77%) of (S)-N-[[3-[3-fluoro-4-(N-(benzyloxyacetamide)-3-pyrrolidinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide as a white foam; mp 53-55°C, MS (CI) [M+H]⁺ 486.

Example 40

(S)-N-[[3-[3-Fluoro-4-(N-(benzyloxyacetamide)pyrrolidinyl-3-oxo)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

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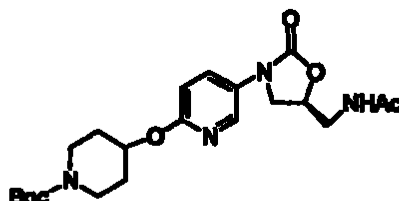


Compound 40

To a solution of 695 mg (1.43 mmol) of Compound 39 in 40 mL MeOH
5 was added 451 mg (7.17 mmol) ammonium formate and a catalytic amount of
10% Pd/C, and the reaction was heated at reflux overnight. Then the
reaction was filtered through a pad of celite and the solvent removed under
reduced pressure. Trituration with EtOAc, MeOH, and hexanes afforded 363
mg (64%) of (S)-N-[[3-[3-fluoro-4-[N-(alpha-hydroxyacetamide)pyrrolidinyl-3-
oxy]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide as a white powder; mp 97-
99°C, MS (CI) [M+H]⁺ 396.

Example 41

(5S)-3-[6-[N-(t-Butoxycarbonyl)piperidinyl-4-oxy]-pyridin-3-yl]-
5-methylacetamide-oxazolidin-2-one



Compound 41

2-[N-(t-Butoxycarbonyl)piperidinyl-4-oxy]-5-nitropyridine:

To a solution of 15.23 g (75.7 mmol) N-(t-butoxycarbonyl)-4-piperidinol
in 450 mL THF at 0°C was added 126 mL (126 mmol) KOtBu and the reaction
stirred for 40 min. Then 10.0 g (63 mmol) 2-chloro-5-nitropyridine was added
and the reaction warmed to rt and stirred overnight. The reaction was diluted
with H₂O, extracted with Et₂O, dried over MgSO₄, filtered, and the solvent
25 removed under reduced pressure to yield the crude product as a black oil.

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Purification by silica gel chromatography (1:1 EtOAc:hexanes) gave the desired product; MS (CI) [M+H]⁺ 324.

2-[N-(t-Butoxycarbonyl)piperidinyl-4-oxy]-5-aminopyridine:

5 A solution of 280 mg (0.87 mmol) of 2-[N-(t-butoxycarbonyl)piperidinyl-4-oxy]-5-nitropyridine in 30 mL of EtOH was treated with a catalytic amount of 10% Pd/C, followed by hydrogenation at 50 psi overnight. The suspension was filtered through celite and the filtrate evaporated under reduced pressure to afford crude amine as a dark solid; MS (CI) [M+H]⁺ 294.

2-[N-(t-Butoxycarbonyl)piperidinyl-4-oxy]-5-(phenylmethoxy carbonylamino)pyrid-3-ine:

10 To a solution of 5.4 g (18.4 mmol) of 2-[N-(t-butoxycarbonyl)piperidinyl-4-oxy]-5-aminopyridine in 300 mL 1:1 THF:H₂O was added 7.18 g (22.1 mmol) cesium carbonate and 3.16 mL (22.1 mmol) benzylchloroformate and the reaction stirred at rt overnight. The mixture was diluted with H₂O, extracted with EtOAc, dried over MgSO₄, filtered, and the solvent removed under reduced pressure to give a dark solid. Purification by silica gel chromatography (4:1 hexanes:EtOAc) yielded 6.5 g (83%) of the carbamate as a yellow solid; MS (CI) [M+H]⁺ 428.

(R)-[3-[6-[N-(t-Butoxycarbonyl)piperidinyl-4-oxy]pyrid-3-yl]-2-oxo-5-oxazolidinyl]methanol:

25 A solution of 5.17 g (12.1 mmol) of 2-[N-(t-butoxycarbonyl)piperidinyl-4-oxy]-3-(phenylmethoxy carbonylamino)pyridine in 250 mL THF was cooled to -78°C and 5.32 mL (13.3 mmol) 2.5 M nBuLi was added and the solution stirred for 1 h. Then 1.89 mL (13.3 mmol) R-glycidal butyrate was added and the reaction allowed to warm to rt and stirred overnight. The reaction was quenched with H₂O, extracted with Et₂O, dried over MgSO₄, filtered, and the solvent removed under reduced pressure to yield 4.22 g (88%) of the alcohol as a brown oil; MS (CI) [M+H]⁺ 394.

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(R)-[3-[4-(N-(t-butoxycarbonyl)piperidinyl-4-oxo)pyrid-3-yl]-2-oxo-5-oxazolidinyl]methanesulfonate:

To a solution of 4.22 g (10.7 mmol) of (R)-[3-[6-(N-(t-butoxycarbonyl)piperidinyl-4-oxo)pyrid-3-yl]-2-oxo-5-oxazolidinyl]methanol in 100 mL CH₂Cl₂ at 0°C was added 2.99 mL (21.4 mmol) NEt₃ and the reaction stirred for 45 min. Then 1.16 mL (15.0 mmol) methanesulfonylchloride was added and the reaction stirred at rt overnight. The reaction was quenched with H₂O, extracted with CH₂Cl₂, dried over MgSO₄, filtered, and the solvent removed under reduced pressure to yield the mesylate as a brown solid.

(R)-[3-[4-(N-(t-butoxycarbonyl)piperidinyl-4-oxo)pyrid-3-yl]-2-oxo-5-oxazolidinyl]methylazide:

To a solution of (R)-[3-[6-(N-(t-butoxycarbonyl)piperidinyl-4-oxo)pyrid-3-yl]-2-oxo-5-oxazolidinyl]methanesulfonate (10.7 mmol) in 100 mL DMF was added 2.78 g (42.8 mmol) sodium azide and the reaction heated at 75°C for 5 h. The reaction was cooled and the solvent removed under reduced pressure. The residue was diluted with H₂O, extracted with EtOAc, dried over MgSO₄, filtered, and the solvent removed under reduced pressure to yield a brown oil which was used crude in the next reaction.

(5S)-3-[6-(N-(t-butoxycarbonyl)piperidinyl-4-oxo)pyridin-3-yl]-5-methylacetamide-oxazolidin-2-one (Compound 41):

A solution of 3.3 g (7.9 mmol) of (R)-[3-[6-(N-(t-butoxycarbonyl)piperidinyl-4-oxo)pyrid-3-yl]-2-oxo-5-oxazolidinyl]methylazide in 30 mL of EtOAc was treated with a catalytic amount of 10% Pd/C, followed by hydrogenation at 50 psi overnight. The suspension was filtered through celite and the filtrate evaporated under reduced pressure to afford crude amine as a dark solid. The crude reaction mixture was treated with 0.47 mL (5.8 mmol) pyridine and 2.39 mL (25 mmol) acetic anhydride and stirred overnight at rt. The volatiles were removed under reduced pressure to give a brown oil. Purification by silica gel chromatography (5% MeOH in EtOAc) yielded 1.7 g of (5S)-3-[6-(N-(t-butoxycarbonyl)piperidinyl-4-oxo)pyridin-3-yl]-

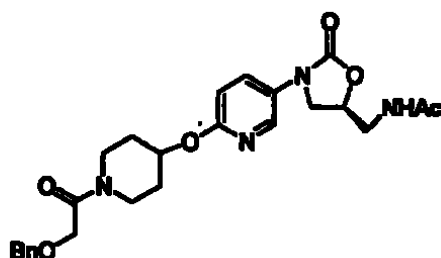
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5-methylacetamide-oxazolidin-2-one as a white foam; mp 99-101°C, MS (CI)[M+H]⁺ 435.

Example 42

5 (5S)-3-[8-[N-(Benzyloxyacetamide)piperidinyl-4-oxy]-pyridin-3-yl]-5-methylacetamide-oxazolidin-2-one



Compound 42

10 ~~(S)-3-[8-[N-(Piperidinyl-4-oxy)pyrid-3-yl]-2-oxo-5-oxazolidinyl] methyl]acetamide:~~

To a solution of 500 mg (1.1 mmol) of Compound 41 in 50 mL CH₂Cl₂ was added 0.88 mL (11.2 mmol) trifluoroacetic acid and the reaction stirred at rt for 3 days. The volatiles were removed under reduced pressure to give the

15 TFA salt as a brown oil.

~~(5S)-3-[8-[N-(Benzyloxyacetamide)piperidinyl-4-oxy]-pyridin-3-yl]-5-methylacetamide-oxazolidin-2-one (Compound 42):~~

A solution of 99 mg (0.18 mmol) of (R)-3-[8-[N-(piperidinyl-4-oxy)pyrid-3-yl]-2-oxo-5-oxazolidinyl] methyl]acetamide in 20 mL CH₂Cl₂ was treated with 0.12 mL (0.88 mmol) NEt₃ and the reaction stirred at rt for 30 min. Then 0.06 mL (0.36 mmol) benzyloxyacetylchloride was added and the reaction stirred overnight. Then 100 mg of PS-Trisamine was added and the suspension stirred for 30 min. The reaction was filtered, quenched with 10 mL H₂O, extracted with CH₂Cl₂ (2 x 20 mL), dried over MgSO₄, and the solvent removed by rotary evaporation to give 31 mg of (5S)-3-[8-[N-(benzyloxyacetamide)piperidinyl-4-oxy]-pyridin-3-yl]-5-methylacetamide-oxazolidin-2-one as a tan semi-solid. ¹H NMR (CDCl₃) δ 8.13 (s, 1H); 7.98 (m, 1H); 7.35 (m, 5H); 6.72 (m, 1H); 6.59 (m, 1H); 5.25 (m, 1H); 4.82 (m, 1H);

189 ~~190~~

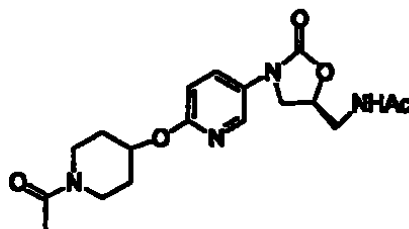
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4.61 (s, 2H); 4.24 (s, 2H); 3.90 (m, 1H); 3.77 (m, 2H); 3.70 (m, 1H); 3.68 (m, 2H); 3.54 (m, 1H); 3.41 (m, 1H); 2.08 (s, 3H); 2.05 (m, 2H); and 1.83 (m, 2H).

Example 43

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(5S)-3-[8-[N-(Acetyl)piperidinyl-4-oxy]-pyridin-3-yl]-5-methylacetamide-oxazolidin-2-one



Compound 43

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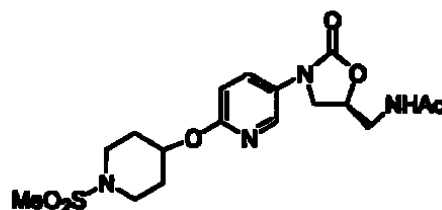
Compound 43 was prepared from 71 mg (0.13 mmol) of the TFA salt from Example 42, 0.09 mL (0.63 mmol) NEt_3 , and 0.02 mL (0.26 mmol) acetyl chloride as described above to give 20 mg of (5S)-3-[8-[N-(acetyl)piperidinyl-4-oxy]-pyridin-3-yl]-5-methylacetamide-oxazolidin-2-one as a white semi-solid. ^1H NMR (CDCl_3) δ 8.14 (m, 1H); 7.95 (m, 1H); 6.77 (s, 1H); 6.76 (brs, 1H); 5.25 (m, 1H); 4.83 (m, 1H); 4.06 (m, 1H); 3.91 (m, 1H); 3.80 (m, 1H); 3.68 (m, 3H); 3.4-3.6 (m, 2H); 2.15 (s, 3H); 2.04 (s, 3H); 2.02 (m, 2H); and 1.77 (m, 2H).

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Example 44

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(5S)-3-[8-[N-(Methanesulfonamide)piperidinyl-4-oxy]-pyridin-3-yl]-5-methylacetamide-oxazolidin-2-one



Compound 44

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Compound 44 was prepared from 56 mg (0.10 mmol) of the TFA salt from Example 42, 0.07 mL (0.50 mmol) NEt_3 , and 0.02 mL (0.20 mmol)

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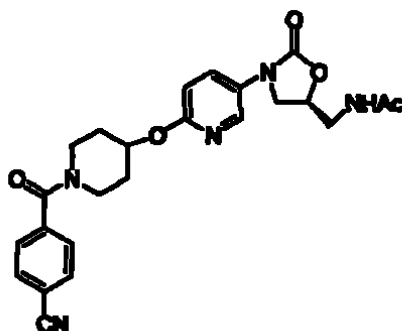
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methanesulfonyl chloride as described above to give 17 mg of (5S)-3-[8-(N-(methanesulfonamide)piperidin-4-oxo)-pyridin-3-yl]-5-methylacetamide-oxazolidin-2-one as a white solid; mp 175-176°C, MS (CI) [M+H]⁺ 413.

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Example 45

(5S)-3-[8-(N-(4-Cyanobenzoyl)piperidin-4-oxo)-pyridin-3-yl]-5-methylacetamide-oxazolidin-2-one



Compound 45

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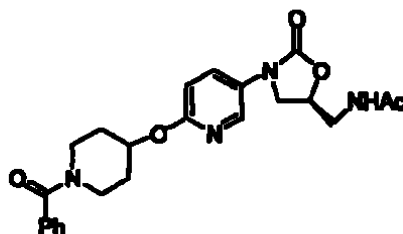
Compound 45 was prepared from 39 mg (0.07 mmol) of the TFA salt from Example 42, 0.05 mL (0.35 mmol) NEt₃, and 23 mg (0.14 mmol) 4-cyanobenzoyl chloride as described above to give 30 mg of (5S)-3-[8-(N-(4-cyanobenzoyl)piperidin-4-oxo)-pyridin-3-yl]-5-methylacetamide-oxazolidin-2-one as a white semi-solid. ¹H NMR (CDCl₃) δ 8.13 (m, 1H); 7.97 (m, 1H); 7.69 (m, 2H); 7.57 (m, 2H); 6.78 (m, 1H); 6.48 (br t, 1H); 5.34 (m, 1H); 4.82 (m, 1H); 4.18 (m, 2H); 3.5-3.8 (m, 5H); 3.37 (m, 1H); 2.03 (s, 3H); 1.97 (m, 2H); and 1.82 (m, 2H).

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Example 46

(5S)-3-[8-(N-(Benzoyl)piperidin-4-oxo)-pyridin-3-yl]-5-methylacetamide-oxazolidin-2-one



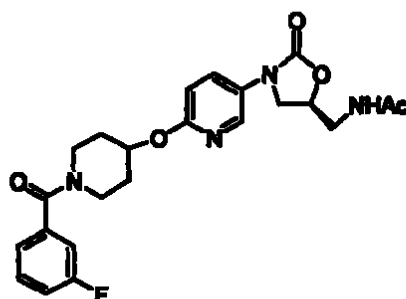
Compound 46

191

Compound 46 was prepared from 48 mg (0.09 mmol) of the TFA salt from Example 42, 0.06 mL (0.43 mmol) NEt_3 , and 0.02 mL (0.20 mmol) benzoyl chloride as described above to give 50 mg of (5S)-3-[6-(N-(benzoyl)piperidin-4-yl)-pyridin-3-yl]-5-methylacetamide-oxazolidin-2-one as a yellow solid; mp 180-182°C, MS (CI) $[\text{M}+\text{H}]^+$ 439.

Example 47

(5S)-3-[6-(N-(3-Fluorobenzoyl)piperidin-4-yl)-pyridin-3-yl]-5-methylacetamide-oxazolidin-2-one

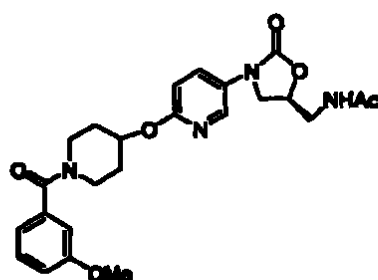


Compound 47

Compound 47 was prepared from 50 mg (0.12 mmol) of the TFA salt from Example 42, 0.08 mL (0.60 mmol) NEt_3 , and 0.03 mL (0.24 mmol) 3-fluorobenzoyl chloride as described above to give 20 mg of (5S)-3-[6-(N-(3-fluorobenzoyl)piperidin-4-yl)-pyridin-3-yl]-5-methylacetamide-oxazolidin-2-one as a clear oil; MS (CI) $[\text{M}+\text{H}]^+$ 457.

Example 48

(5S)-3-[6-(N-(3-Methoxybenzoyl)piperidin-4-yl)-pyridin-3-yl]-5-methylacetamide-oxazolidin-2-one



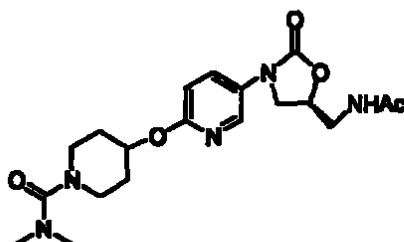
Compound 48

192 ~~193~~

Compound 48 was prepared from 50 mg (0.12 mmol) of the TFA salt from Example 42, 0.08 mL (0.60 mmol) NEt_3 , and 0.03 mL (0.24 mmol) 3-methoxybenzoyl chloride as described above to give 20 mg of (5S)-3-[8-(N-(3-methoxybenzoyl)piperidin-4-yl)-pyridin-3-yl]-5-methylacetamide-oxazolidin-2-one as a yellow oil; MS (CI) $[\text{M}+\text{H}]^+$ 488.

Example 49

(5S)-3-[8-(N-(Dimethylcarbamoyl)piperidin-4-yl)-pyridin-3-yl]-5-methylacetamide-oxazolidin-2-one

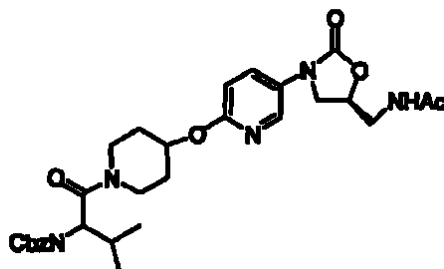


Compound 49

Compound 49 was prepared from 50 mg (0.12 mmol) of the TFA salt from Example 42, 0.08 mL (0.60 mmol) NEt_3 , and 0.02 mL (0.24 mmol) dimethylcarbamoyl chloride as described above to give 17 mg of (5S)-3-[8-(N-(dimethylcarbamoyl)piperidin-4-yl)-pyridin-3-yl]-5-methylacetamide-oxazolidin-2-one as a white semi-solid; MS (CI) $[\text{M}+\text{H}]^+$ 408.

Example 50

(5S)-3-[8-(N-(CBZ-valine)piperidin-4-yl)-pyridin-3-yl]-5-methylacetamide-oxazolidin-2-one



Compound 50

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H

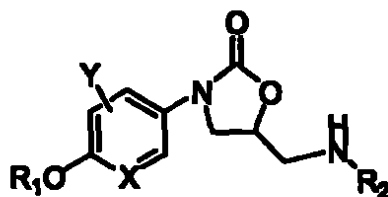
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To a solution of 36 mg (0.06 mmol) of the TFA salt from Example 42 in 20 mL CH_2Cl_2 was added 32 mg (0.13 mmol) Cbz-VAL-OH, 13 mg (0.07 mmol) EDCI, and 35 mg (0.25 mmol) HOBT. The reaction stirred at rt overnight. Then the solution was washed with H_2O , extracted with CH_2Cl_2 , washed with sat. NaHCO_3 , dried with MgSO_4 , and concentrated to give 10 mg of (5S)-3-[6-[N-(CBZ-valine)piperidin-4-oxy]-pyridin-3-yl]-5-methylacetamide-oxazolidin-2-one as a clear oil. ^1H NMR (CDCl_3) δ 8.10 (m, 1H); 7.99 (m, 1H); 7.37 (m, 5H); 6.76 (m, 1H); 6.20 (m, 1H); 5.33 (s, 2H); 5.19 (m, 1H); 5.11 (m, 1H); 4.82 (m, 1H); 4.08 (m, 1H); 3.79 (m, 2H); 3.5-3.7 (m, 4H); 3.25 (m, 1H); 2.97 (m, 1H); 2.13 (m, 2H); 2.08 (s, 3H); 1.84 (m, 2H); and 1.30 (s, 6H).

The invention has been described in detail with particular reference to the above embodiments thereof. The above embodiments and examples are given to illustrate the scope and spirit of the present invention. These embodiments and examples will make apparent, to those skilled in the art, other embodiments and examples. These other embodiments and examples are within the contemplation of the present invention. It will be understood that variations and modifications can be effected within the spirit and scope of the invention; therefore, the instant invention should be limited only by the appended claims.

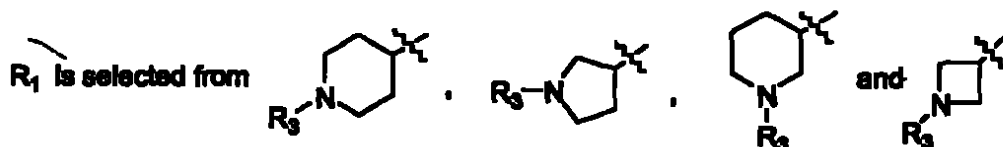
We claim:

1. A compound of Formula I



Formula I

wherein



wherein

(a) R_3 is selected from H, alkyl, $-\text{COR}_4$, $-(\text{CH}_2)_t\text{heteroaryl}$, $-\text{CHR}_4\text{R}_5$, $-(\text{CH}_2)_t\text{aryl}$, $-\text{SO}_2\text{NR}_5\text{R}_6$, and $-\text{SO}_2\text{R}_6$;

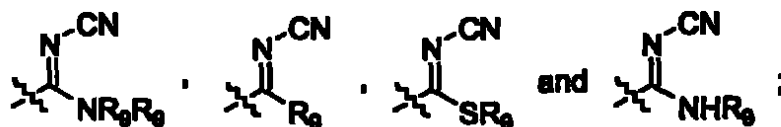
(b) R_4 is selected from H, $-\text{OR}_6$, alkyl, alkylaryl, $-(\text{CH}_2)_t\text{aryl}$, $-(\text{CH}_2)_t\text{heteroaryl}$, $-(\text{CH}_2)_t\text{OR}_6$, $-(\text{CH}_2)_t\text{NR}_7\text{R}_8$, $-\text{CHR}_6\text{R}_8$, and $-\text{NR}_6\text{R}_8$ optionally forming a cyclic amino derivative;

(c) R_5 and R_6 are independently selected from H, alkyl, alkylaryl, haloaryl, $-(\text{CH}_2)_t\text{aryl}$, $-(\text{CH}_2)_t\text{heteroaryl}$, and amido;

(d) R_7 and R_8 are independently selected from H, alkyl, $-\text{COR}_9$, $-\text{SO}_2\text{R}_9$ and $-\text{CO}_2\text{R}_9$; and

(e) R_9 is selected from H, alkyl, aryl and alkylaryl;

R_2 is selected from $\text{C}(\text{O})\text{R}_9$, $\text{C}(\text{O})\text{OR}_9$,



X is N or CH;

Y is selected from H, halogen, alkoxy, and alkyl;

t is an integer of 0 to 4;

195 *pk*

or an optical isomer, enantiomer, diastereomer, racemate or racemic mixture thereof, or a pharmaceutically acceptable salt thereof.

2. The compound of Claim 1 wherein X is CH.

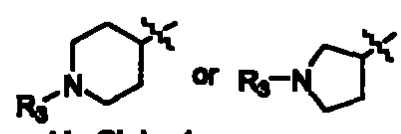
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3. The compound of Claim 1 wherein R_2 is $-C(O)OR_3$ wherein R_3 is as claimed in Claim 1.

4. The compound of Claim 3 wherein R_3 is H or alkyl.

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5. The compound of Claim 1 wherein R_1 is



wherein R_3 is as claimed in Claim 1.

15

6. The compound of Claim 5 wherein R_4 is selected from $-COR_5$, $-SO_2R_5$ and $-(CH_2)_t$ heteroaryl wherein R_5 and t are as claimed in Claim 1.

7. The compound of Claim 5 wherein R_4 is selected from $-OR_5$, alkyl, $-(CH_2)_t$ aryl, and $-(CH_2)_t$ heteroaryl wherein R_5 and t are as claimed in Claim 1.

20

8. The compound of Claim 7 wherein R_5 is alkyl and R_6 is H or alkyl.

9. A compound of Claim 1 or a pharmaceutically acceptable salt thereof, which is (S)-N-[[3-[3-fluoro-4-[N-(benzyloxyacetamide)piperidinyl-4-oxy]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

25

10. A compound of Claim 1 or a pharmaceutically acceptable salt thereof, which is (S)-N-[[3-[3-fluoro-4-[N-(α -hydroxyacetamide)piperidinyl-4-oxy]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

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11. A compound of Claim 1 or a pharmaceutically acceptable salt thereof, which is (S)-N-[[3-[3-fluoro-4-(N-(methanesulfonamide)piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

5 12. A compound of Claim 1 or a pharmaceutically acceptable salt thereof, which is (S)-N-[[3-[3-fluoro-4-(N-(methylester)piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

10 13. A compound of Claim 1 or a pharmaceutically acceptable salt thereof, which is (S)-N-[[3-[3-fluoro-4-(N-(2-pyrimidine)piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

15 14. A compound of Claim 1 or a pharmaceutically acceptable salt thereof, which is (S)-N-[[3-[3-fluoro-4-(N-(3-cyanobenzoyl)piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

20 15. A compound of Claim 1 of a pharmaceutically acceptable salt thereof, which is (S)-N-[[3-[3-fluoro-4-(N-(5-cyano-2-pyridyl)piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

16 16. A compound of Claim 1 or a pharmaceutically acceptable salt thereof, which is (S)-N-[[3-[3-fluoro-4-(N-(2-thiophenylcarbonyl)piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

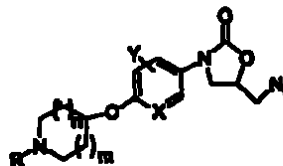
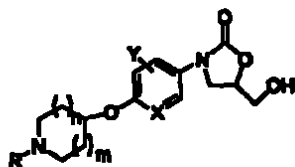
25 17. A compound of Claim 1 or a pharmaceutically acceptable salt thereof, which is (S)-N-[[3-[3-fluoro-4-(N-(α -hydroxyacetamide)piperidinyl-3-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

30 18. A compound of Claim 1 or a pharmaceutically acceptable salt thereof, which is (S)-N-[[3-[3-Fluoro-4-(N-(benzyloxyacetamide)pyrrolidinyl-3-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

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19. A pharmaceutical composition comprising a compound of Claim 1 and a pharmaceutically acceptable carrier.
20. A method of treating a subject having a condition caused by or contributed to by bacterial infection, which comprises administering to said subject a therapeutically effective amount of the compound of Formula I as defined in Claim 1.
21. A method of preventing a subject from suffering from a condition caused by or contributed to by bacterial infection, which comprises administering to the subject a prophylactically effective amount of the compound of Formula I as defined in Claim 1.
22. The method of Claim 20 or 21 wherein said condition is selected from community-acquired pneumonia, upper and lower respiratory tract infections, skin and soft tissue infections, bone and joint infections, and hospital-acquired lung infections.
23. The method of Claim 20 or 21 wherein said bacterium is selected from *S. aureus*, *S. epidermidis*, *S. pneumoniae*, *Enterococcus* spp., *Moraxella catarrhalis* and *H. influenzae*.
24. The method of Claim 20 or 21 wherein said bacterium is a Gram-positive coccus.
25. The method of Claim 24 wherein said Gram-positive coccus is antibiotic-resistant.
26. An intermediate of Formula e or f



wherein

R is Boc, $-\text{CH}(\text{Ph})_2$ or $-\text{COCH}_2\text{OCH}_2\text{Ph}$;

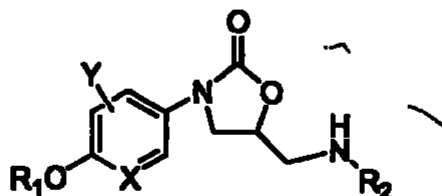
X is N or CH;

5 Y is selected from H, halogen, alkoxy, and alkyl;

n is 0, 1 or 2; and

m is 0 or 1.

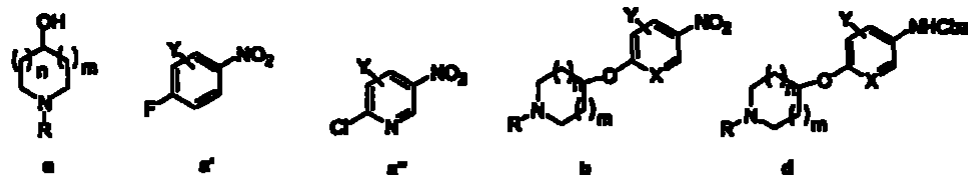
27. A process for preparing a compound of Formula I



Formula I

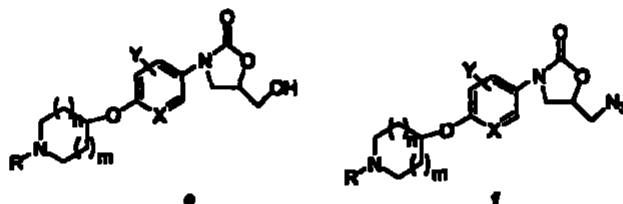
wherein R_1 , R_2 , X, and Y are as claimed in Claim 1 and R, m, and n are as claimed in Claim 26, which process comprises:

(a) reacting a compound of Formula a with a compound of Formula a' or a'' to form a compound of Formula b;



(b) converting the compound of Formula b to a compound of Formula d;

(c) reacting the compound of Formula d with  to form a compound of Formula e;

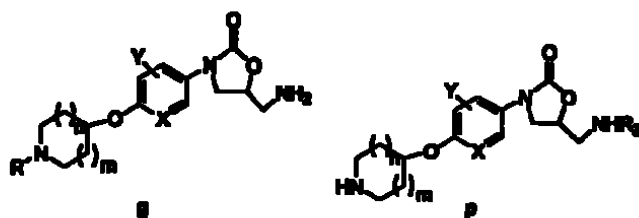


(d) converting the compound of Formula e to a compound of Formula f;

(e) converting the compound of Formula f to a compound of Formula g;

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- (f) converting the compound of Formula f to a compound of Formula g; and
 (g) converting the compound of Formula p to a compound of Formula i.

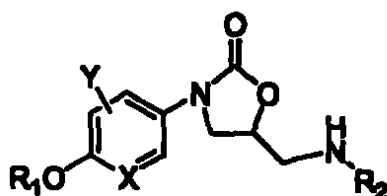
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Piperidin I and Pyrrolidin I Oxazolidinone Antibacterials

Abstract

5

Piperidinol, pyrrolidinol and azetidinol compounds of the formula:



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wherein R₁ is a piperidinol, pyrrolidinol or azetidinol moiety as described herein and in which the substituents have the meaning indicated in the description. These compounds are useful as antibacterial agents.

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**ESTADOS UNIDOS DE AMERICA
A TODOS AQUELLOS A QUIENES EL PRESENTE
LLEGUE:**

**DEPARTAMENTO DE COMERCIO DE LOS ESTADOS
UNIDOS
Oficina de Patentes y Marcas de los Estados Unidos**

Febrero 12, 2001

La presente es para certificar que el anexo es una copia fiel de los registros de la Oficina de Patentes y Marcas de los Estados Unidos, de los documentos de la solicitud de patente identificada más adelante, que cumplieron con los requerimientos para concederse una fecha de presentación de acuerdo con 35 USC 111.

Número de Solicitud: 09/729,342

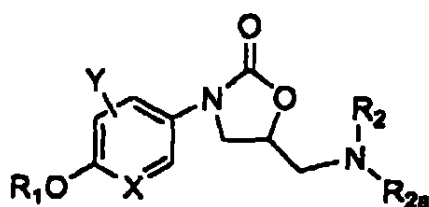
Fecha de Presentación: Diciembre 5, 2000

**Por la autoridad del
Comisionado de Patentes y Marca**

**(fdo) H.L. JACKSON
Oficial Certificador
Sello oficial de la Oficina de Patentes y Marcas de los
Estados Unidos de América**

REIVINDICACIONES

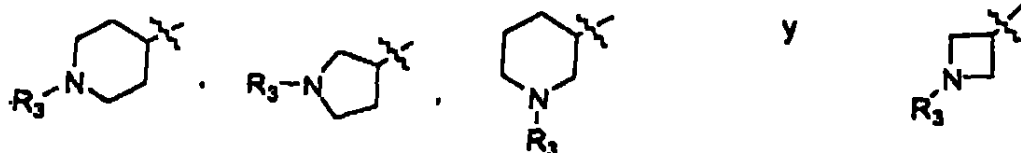
1. Un compuesto de Fórmula I



Fórmula I

en donde

R₁ se selecciona entre



en donde

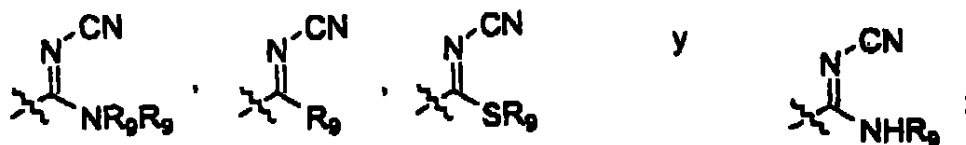
(a) R₃ se selecciona entre H, alquilo, -COR₄, -(CH₂)_theteroarilo, -CHR₅R₆, -(CH₂)_tarilo, -SO₂NR₅R₆ y -SO₂R₉;

(b) R₄ se selecciona entre H, -OR₅, alquilo, alquilarilo, -(CH₂)_tarilo, -(CH₂)_theteroarilo, -(CH₂)_tOR₆, -(CH₂)_tNR₇R₈, -CHR₅R₆ y -NR₅R₆ opcionalmente formando un derivado amino cíclico;

(c) R₅ y R₆ se seleccionan independientemente entre H, alquilo, alquilarilo, haloarilo, -(CH₂)_tarilo, -(CH₂)_theteroarilo y acilo;

(d) R_7 y R_8 se seleccionan independientemente entre H, alquilo, $-\text{COR}_9$, $-\text{SO}_2\text{R}_9$ y $-\text{CO}_2\text{R}_9$; y

(e) R_9 se selecciona entre H, alquilo, arilo y alquilarilo;
 R_2 se selecciona entre $\text{C}(\text{O})\text{R}_9$, $\text{C}(\text{O})\text{OR}_9$,



R_{2a} es H o acilo, con la condición que cuando R_3 se selecciona entre alquilo, $-(\text{CH}_2)_t\text{arilo}$, $-(\text{CH}_2)_t\text{heteroarilo}$ y $-\text{CHR}_9\text{R}_9$, R_{2a} es H;

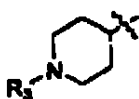
X es N o CH;

Y se selecciona entre H, halógeno, alcoxi y alquilo; y

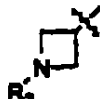
t es un entero de 0 a 4;

o un isómero óptico, enantiómero, diastereómero, racemato o mezcla racémica de los mismos, o una sal farmacéuticamente aceptable de los mismos.

2. El compuesto de la reivindicación 1, en donde X es CH.
3. El compuesto de la reivindicación 1, en donde R_2 es $-\text{C}(\text{O})\text{R}_9$, en donde R_9 es como se reivindica en la reivindicación 1.
4. El compuesto de la reivindicación 3, en donde R_9 es H o alquilo.
5. El compuesto de la reivindicación 1, en donde R_1 es



o



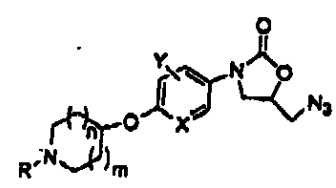
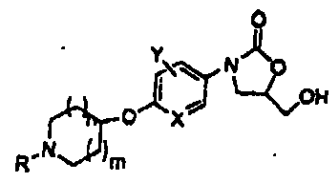
, en donde R_3 es como se reivindica en la reivindicación 1.

6. El compuesto de la reivindicación 5, en donde R_{2a} es H, y R_3 se selecciona entre $-COR_4$, $-SO_2R_5$ y $-(CH_2)_t$ heteroarilo, en donde R_4 , R_5 y t son como se reivindican en la reivindicación 1.
7. El compuesto de la reivindicación 5, en donde R_4 se selecciona entre $-OR_5$, $-(CH_2)_tOR_5$, alquilo, $-(CH_2)_t$ arilo y $-(CH_2)_t$ heteroarilo, en donde R_5 y t son como se reivindican en la reivindicación 1.
8. El compuesto de la reivindicación 7, en donde R_5 es alquilo, y R_4 es H o alquilo.
9. Un compuesto de la reivindicación 1 o una sal farmacéuticamente aceptable del mismo, que es (S)-N-[[3-[3-fluoro-4-{N-(benciloxiacetil)piperidinil-4-oxi}fenil]-2-oxo-5-oxazolidinil]metil]acetamida.
10. Un compuesto de la reivindicación 1 o una sal farmacéuticamente aceptable del mismo, que es (S)-N-[[3-[3-fluoro-4-{N-(α -hidroxiacetil)piperidinil-4-oxi}fenil]-2-oxo-5-oxazolidinil]metil]acetamida.
11. Un compuesto de la reivindicación 1 o una sal farmacéuticamente aceptable del mismo, que es (S)-N-[[3-[3-fluoro-4-{N-(metanosulfonil)piperidinil-4-oxi}fenil]-2-oxo-5-oxazolidinil]metil]acetamida.
12. Un compuesto de la reivindicación 1 o una sal farmacéuticamente aceptable del mismo, que es (S)-N-[[3-[3-fluoro-4-{N-(metoxycarbonil)piperidinil-4-oxi}fenil]-2-oxo-5-oxazolidinil]metil]acetamida.
13. Un compuesto de la reivindicación 1 o una sal farmacéuticamente aceptable del mismo, que es (S)-N-[[3-[3-fluoro-4-{N-(2-pirimidinil)piperidinil-4-oxi}fenil]-2-oxo-5-oxazolidinil]metil]acetamida.
14. Un compuesto de la reivindicación 1 o una sal farmacéuticamente aceptable del mismo, que es (S)-N-[[3-[3-fluoro-4-{N-(3-cianobenzolil)piperidinil-4-oxi}fenil]-2-oxo-5-oxazolidinil]metil]acetamida.

15. Un compuesto de la reivindicación 1 o una sal farmacéuticamente aceptable del mismo, que es (S)-N-[[3-[3-fluoro-4-{N-(5-ciano-2-piridil)piperidinil-4-oxi}fenil]-2-oxo-5-oxazolidinil]metil]acetamida.
16. Un compuesto de la reivindicación 1 o una sal farmacéuticamente aceptable del mismo, que es (S)-N-[[3-[3-fluoro-4-{N-(2-fenilcarbonyl)piperidinil-4-oxi}fenil]-2-oxo-5-oxazolidinil]metil]acetamida.
17. Un compuesto de la reivindicación 1 o una sal farmacéuticamente aceptable del mismo, que es (S)-N-[[3-[3-fluoro-4-{N-(α -hidroxilacetil)piperidinil-3-oxi}fenil]-2-oxo-5-oxazolidinil]metil]acetamida.
18. Un compuesto de la reivindicación 1 o una sal farmacéuticamente aceptable del mismo, que es (S)-N-[[3-[3-fluoro-4-{N-(benciloxiacetil)pirrolidinil-3-oxi}fenil]-2-oxo-5-oxazolidinil]metil]acetamida.
19. Una composición farmacéutica que comprende un compuesto de la reivindicación 1 y un portador farmacéuticamente aceptable.
20. Un método de tratamiento de un sujeto que tiene una condición causada o que es contribuida por una infección bacteriana, que comprende administrar a dicho sujeto una cantidad terapéuticamente efectiva del compuesto de Fórmula I como se define en la reivindicación 1.
21. Un método de prevención para un sujeto que sufre de una condición causada o que es contribuida por una infección bacteriana, que comprende administrar al sujeto una cantidad profilácticamente efectiva del compuesto de Fórmula I como se define en la reivindicación 1.
22. El método de la reivindicación 20 ó 21, en donde dicha condición se selecciona entre neumonía adquirida por la comunidad, infecciones del tracto respiratorio superior e inferior, infecciones del tejido blando y piel, infecciones de articulaciones y huesos e infecciones pulmonares adquiridas en hospitales.

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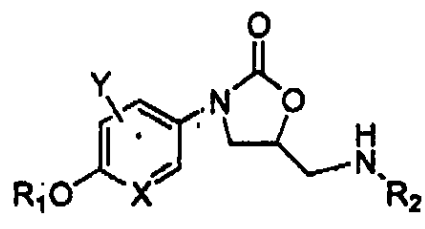
23. El método de la reivindicación 20 ó 21, en donde dicha bacteria se selecciona entre *S. aureus*, *S. epidermidis*, *S. pneumoniae*, *Enterococcus spp.*, *Moraxella catarrhalis* y *H. influenzae*.
24. El método de la reivindicación 20 ó 21, en donde dicha bacteria es un coco Gram-positivo.
25. El método de la reivindicación 24, en donde dicho coco Gram-positivo es resistente a antibióticos.
26. Un intermediario de Fórmula e o f



en donde

- R es Boc, -CH(Ph)₂ o -COCH₂OCH₂Ph;
- X es N o CH;
- Y se selecciona entre H, halógeno, alcoxi y alquilo;
- n es 0, 1 ó 2; y
- m es 0 ó 1.

27. Un proceso para la preparación de un compuesto de Fórmula la



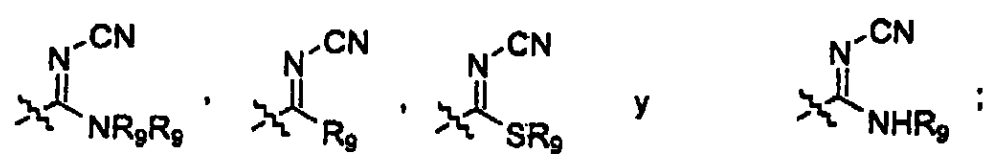
Fórmula la

en donde R_1 es una porción de la fórmula:



en donde:

R se selecciona entre Boc, $-\text{CH}(\text{Ph})_2$ o $-\text{COCH}_2\text{OCH}_2\text{Ph}$, n es 0, 1 ó 2, m es 0 ó 1,
 R_2 , se selecciona entre $\text{C}(\text{O})\text{R}_9$, $\text{C}(\text{O})\text{OR}_9$.

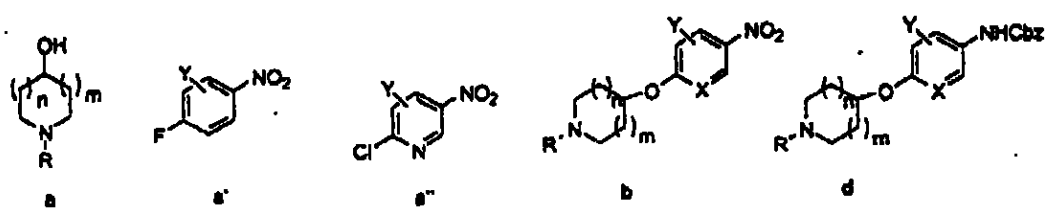


en donde R_9 se selecciona entre H, alquilo, arilo y alquilarilo; X es N o CH;

Y se selecciona entre H, halógeno, alcoxi y alquilo;

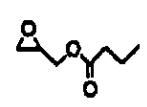
cuyo proceso comprende:

(a) hacer reaccionar un compuesto de Fórmula a con un compuesto de Fórmula a' o a'' para formar un compuesto de Fórmula b;

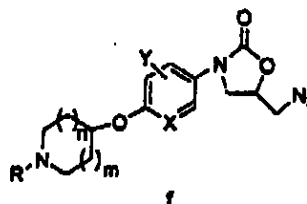
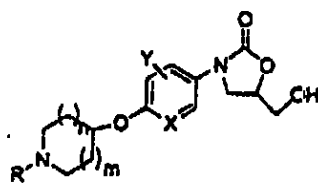


(b) convertir el compuesto de Fórmula b en un compuesto de Fórmula d;

(c) hacer reaccionar el compuesto de Fórmula d con

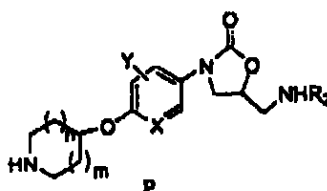
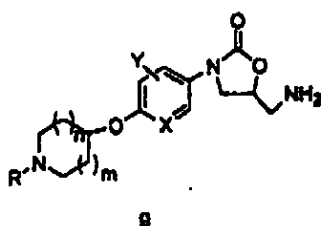


para formar un compuesto de Fórmula e;



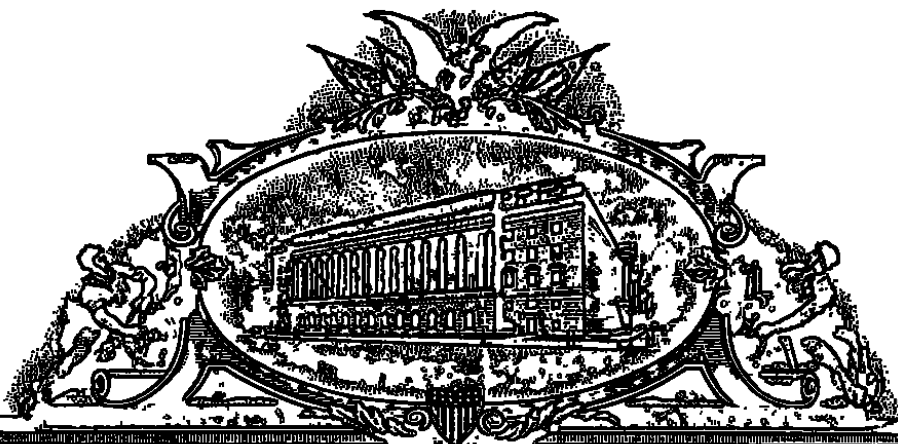
(d) convertir el compuesto de Fórmula e en un compuesto de Fórmula f;

(e) convertir el compuesto de Fórmula f en un compuesto de Fórmula g;



(f) convertir el compuesto de Fórmula g en un compuesto de Fórmula p; y

(g) convertir el compuesto de Fórmula p en un compuesto de Fórmula la.



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THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

February 12, 2001

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 UNDER 35 USC 111.

APPLICATION NUMBER: 09/729,342

FILING DATE: December 05, 2000



By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

H. L. JACKSON
Certifying Officer

Please type a plus sign (+) inside this box ☐

UTILITY
PATENT APPLICATION
TRANSMITTAL

Attorney Docket No.

ORT-1330

First Named Inventor or Application Identifier

Michele A. Weidner-Wells, Christine Boggs, Dennis Hlasta and Eric Nelson

Express Mail Label No.

(only for new nonprovisional applications under 37 CFR 1.53(b))

12/05/00
09/729342
S. PTO

APPLICATION ELEMENTS

ADDRESS TO:

Assistant Commissioner for Patents
Box Patent Application
Washington, DC 20231

See MPEP Chapter 800 concerning utility patent application contents.

1. ☒ Fee Transmittal Form (attached hereto in duplicate)

2. ☒ Specification [Total Pages 84]

(Preferred arrangement set forth below)

- Descriptive Title of the Invention
- Cross References to Related Applications
- Statement Regarding Fed sponsored R&D
- Reference to Microfiche Appendix
- Background of the Invention
- Brief Summary of the Invention
- Brief Description of the Drawings (if filed)
- Detailed Description
- Claim(s)
- Abstract of the Disclosure

☐ Drawing(s) (35 USC 113) [Total Sheets]

Oath or Declaration

- a. ☒ Newly executed (original or copy)
- b. ☐ Unexecuted original
- c. ☐ Copy from a prior application (37 CFR 1.63(d))
(for continuation/divisional check boxes 5 and 16)
 - i. ☐ Deletion of Inventor(s)
Signed statement attached deleting inventor(s) named in the prior application, see 37 CFR 1.63(d)(2) and 1.33(b).

☐ Incorporation by Reference
(useable if Box 4c is checked)
The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied under Box 4c, is considered as being part of the disclosure of the accompanying application and is hereby incorporated by reference therein.

6. ☐ Microfiche Computer Program (Appendix)

7. Nucleotide and/or Amino Acid Sequence Submission (if applicable, all necessary)

- a. ☐ Computer Readable Copy
- b. ☐ Paper Copy (identical to computer copy)
- c. ☐ Statement verifying identity of above copies

ACCOMPANYING APPLICATION PARTS

- 8. ☒ Assignment Papers (cover sheet & document(s)) (signed)
- 9. ☐ 37 CFR 3.73(b) Statement (when there is an assignee) ☐ Power of Attorney
- 10. ☐ English Translation Document (if applicable)
- 11. ☐ Information Disclosure Statement (IDS) PTO-1449 ☐ Copies of IDS Citations
- 12. ☐ Preliminary Amendment
- 13. ☒ Return Receipt Postcard (MPEP 503) (Should be specifically itemized)
- 14. ☐ Certified Copy of Priority Document(s) (if foreign priority is claimed)

15. ☐ Other:

16. ☐ If a CONTINUING APPLICATION, check appropriate box and supply the requisite information:

Amend the specification by inserting before the first line: -- This is a ☐ Continuation ☐ Divisional

☐ Continuation-in-Part (CIP) of prior application No.:

17. For this divisional application, please cancel original Claims of the prior application before calculating the filing fee.

18. CORRESPONDENCE ADDRESS

☐ Customer Number or Bar Code Label

or ☒ Correspondence Address below

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Telephone: (732) 524-2641 Fax: (732) 524-2808

19. SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

NAME

Kenneth J. Dow

Reg. No. 32,890

SIGNATURE

DATE

December 7, 2000

FEE TRANSMITTAL	Complete if Known	
	Application Number	
	Filing Date	
	First Named Inventor	Michele A. Weidner-Wells
	Group Art Unit	
	Examiner Name	
	Attorney Docket Number	ORT-1330

CLAIMS AS FILED

(1)	(2)	(3)	(4)	(5)
FOR:	NUMBER FILED	NUMBER EXTRA	RATE	BASIC FEE \$710.00
TOTAL CLAIMS	27 - 20 =	7	x 18.00	\$ 126.00
INDEPENDENT CLAIMS	3 - 3 =	0	x 80.00	\$ 0.00
MULTIPLE DEPENDENT CLAIMS	☐	N/A	\$270.00	
			TOTAL FEES	\$ 836.00

☒ Please charge Deposit Account No. 10-0750/ORT1330/KJD in the amount of \$836.00.
Three copies of this sheet are enclosed.

- ☒ The Commissioner is hereby authorized to charge any additional fees which may be required in connection with the filing of this communication, or credit any overpayment, to Account No. 10-0750/ORT1330/KJD. Three copies of this sheet are enclosed.

SUBMITTED BY:		<i>Complete (if applicable)</i>
Typed or Printed Name	Kenneth J. Dow	Reg. No. 32,890
Signature		Deposit Account No. 10-0750
	Date: December 4, 2000	

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Piperidinyloxy and Pyrrolidinyloxy Oxazolidinone Antibacterials

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FIELD OF THE INVENTION

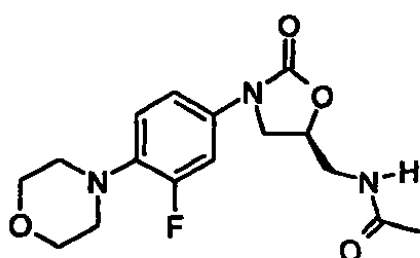
The present invention relates to the field of piperidinyloxy, pyrrolidinyloxy and azetidinyloxy oxazolidinone compounds having antibacterial activity, pharmaceutical compositions containing the compounds, and methods of treating bacterial infections with the compounds.

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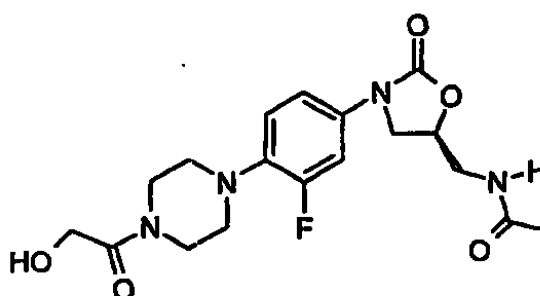
BACKGROUND OF THE INVENTION

Oxazolidinones have been identified, within the last twenty years, as a new class of antibacterials which are active against numerous multidrug-resistant gram positive organisms. Particularly problematic pathogens include methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE) and penicillin- and cephalosporin-resistant *Streptococcus pneumoniae*. As a class oxazolidinones exhibit a unique mechanism of action. Studies have shown that these compounds selectively bind to the 50S ribosomal subunit and inhibit bacterial translation at the initiation phase of protein synthesis. Exemplary members of oxazolidinones are linezolid (see WO 95/07271) and eperezolid.

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linezolid



eperezolid

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The following references relate to various oxazolidinone type compounds disclosed as having antibacterial activity:

U.S. Pat. No. 4,705,799 to W. A. Gregory discloses aminomethyl oxoxazolidinyl benzene derivatives, including the sulfides, sulfoxides, sulfones and sulfonamides, such as (1)-N-[3-[4-(methylsulfinyl)-phenyl]-2-oxoxazolidin-5-ylmethyl]acetamide.

U.S. Pat. No. 5,565,571 to Barbachyn et al. discloses substituted aryl- and heteroarylphenyloxazolidinones.

U.S. Pat. No. 5,792,765 to Riedl et al. relates to new substituted oxazolidinones.

U.S. Pat. No. 5,910,504 to Hutchinson discloses phenyloxazolidinone compounds having a nitrogen containing hetero-aromatic ring substitution attached through one of the nitrogen atoms.

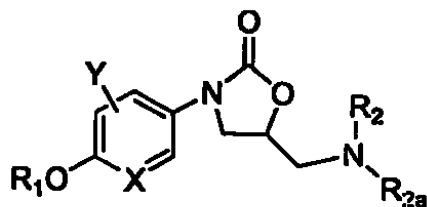
WO 93/09103 (Barbachyn et al.) discloses substituted aryl- and heteroarylphenyloxazolidinones.

WO 95/07271 (Barbachyn et al.) discloses oxazine and thiazine oxazolidinone derivatives.

WO 98/54161 (Hester et al.) provides oxazolidinone antibacterial agents having a thiocarbonyl functionality.

SUMMARY OF THE INVENTION

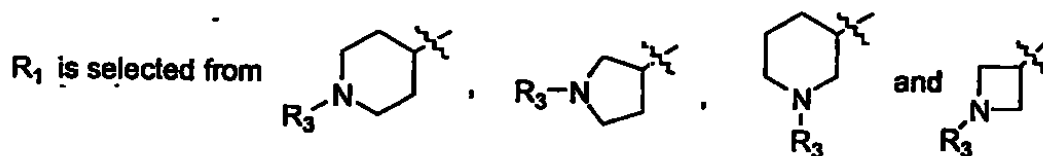
The invention provides new piperidinyloxy, pyrrolidinyloxy and azetidinyloxy compounds of Formula I



Formula I

wherein

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wherein

(a) R_3 is selected from H, alkyl, $-\text{COR}_4$, $-(\text{CH}_2)_t\text{heteroaryl}$, $-\text{CHR}_5\text{R}_6$, $-(\text{CH}_2)_t\text{aryl}$, $-\text{SO}_2\text{NR}_5\text{R}_6$, and $-\text{SO}_2\text{R}_9$;

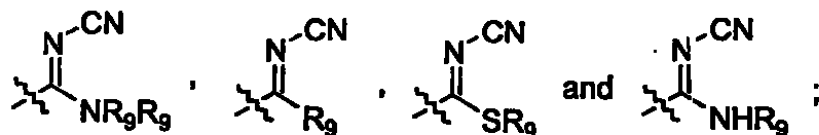
5 (b) R_4 is selected from H, $-\text{OR}_6$, alkyl, alkylaryl, $-(\text{CH}_2)_t\text{aryl}$, $-(\text{CH}_2)_t\text{heteroaryl}$, $-(\text{CH}_2)_t\text{OR}_5$, $-(\text{CH}_2)_t\text{NR}_7\text{R}_8$, $-\text{CHR}_5\text{R}_6$, and $-\text{NR}_5\text{R}_6$ optionally forming a cyclic amino derivative;

(c) R_5 and R_6 are independently selected from H, alkyl, alkylaryl, haloaryl, $-(\text{CH}_2)_t\text{aryl}$, $-(\text{CH}_2)_t\text{heteroaryl}$, and acyl;

(d) R_7 and R_8 are independently selected from H, alkyl, $-\text{COR}_9$, $-\text{SO}_2\text{R}_9$ and $-\text{CO}_2\text{R}_9$; and

(e) R_9 is selected from H, alkyl, aryl and alkylaryl;

R_2 is selected from $\text{C}(\text{O})\text{R}_9$, $\text{C}(\text{O})\text{OR}_9$,



R_{2a} is H or acyl with the proviso that when R_3 is selected from alkyl, $-(\text{CH}_2)_t\text{aryl}$, $-(\text{CH}_2)_t\text{heteroaryl}$, and $-\text{CHR}_5\text{R}_6$, R_{2a} is H;

20 X is N or CH;

Y is selected from H, halogen, alkoxy, and alkyl; and

t is an integer of 0 to 4;

or an optical isomer, enantiomer, diastereomer, racemate or racemic mixture thereof, or a pharmaceutically acceptable salt thereof.

Compounds of the above formula are useful as antibacterial agents for the treatment of bacterial infections in a subject such as human and animal.

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The present invention is also directed to a method of treating a subject having a condition caused by or contributed to by bacterial infection, which comprises administering to said subject a therapeutically effective amount of the compound of Formula I.

The present invention is further directed to a method of preventing a subject from suffering from a condition caused by or contributed to by bacterial infection, which comprises administering to the subject a prophylactically effective amount of the compound of Formula I.

Other objects and advantages will become apparent to those skilled in the art from a review of the ensuing specification.

DETAILED DESCRIPTION

Relative to the above description, certain definitions apply as follows.

Unless otherwise noted, under standard nomenclature used throughout this disclosure the terminal portion of the designated side chain is described first, followed by the adjacent functionality toward the point of attachment.

Unless specified otherwise, the terms "alkyl", "alkenyl", and "alkynyl," whether used alone or as part of a substituent group, include straight and branched chains having 1 to 8 carbon atoms, or any number within this range. For example, alkyl radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl, 3-(2-methyl)butyl, 2-pentyl, 2-methylbutyl, neopentyl, n-hexyl, 2-hexyl and 2-methylpentyl. "Alkoxy" radicals are oxygen ethers formed from the previously described straight or branched chain alkyl groups. "Cycloalkyl" groups contain 3 to 8 ring carbons and preferably 5 to 7 ring carbons. The alkyl group and alkoxy group may be independently substituted with one or more members of the group including, but not limited to, mono-, di-,

tri-, or per-halogen, alkyl, alkoxy, aryl, heteroaryl, heterocyclyl, amino, substituted amino, OH, CN, mercapto, nitro, and C₁₋₈ acyloxy.

5 The term "acyl" as used herein, whether used alone or as part of a substituent group, means an organic radical having 2 to 6 carbon atoms (branched or straight chain) derived from an organic acid by removal of the hydroxyl group.

The term "Ac" as used herein means acetyl.

10 The term "halo" or "halogen" means fluoro, chloro, bromo and iodo. (Mono-, di-, tri-, and per-)halo-alkyl is an alkyl radical substituted by independent replacement of the hydrogen atoms thereon with halogen.

15 "Aryl" or "Ar," whether used alone or as part of a substituent group, is a carbocyclic aromatic radical including, but not limited to, phenyl, 1- or 2- naphthyl and the like. The carbocyclic aromatic radical may be substituted by independent replacement of 1 to 3 of the hydrogen atoms thereon with halogen, -OH, -CN, mercapto, nitro, amino, substituted amino, alkyl, -O-alkyl, -S-alkyl, -NH-alkyl, -N(alkyl)₂, (mono-, di-, tri-, and per-) halo-alkyl, formyl, -COR_s, -COOR_s, -CONHR_s, -CONR_sR_s, -SOR_s, -SO₂R_s, -SO₂NHR_s, -SO₂NR_sR_s, alkyl-COO, alkyl-CONH, or carboxamide or a second aryl ring, wherein R_s and R_t are defined as hereinabove. Illustrative aryl radicals include, for example, phenyl, naphthyl, diphenyl, fluorophenyl, difluorophenyl, benzyl, benzoyloxyphenyl, carboethoxyphenyl, acetylphenyl, ethoxyphenyl, phenoxyphenyl, hydroxyphenyl, 20 carboxyphenyl, trifluoromethylphenyl, methoxyethylphenyl, acetamidophenyl, tolyl, xylyl, dimethylcarbamylphenyl and the like. "Ph" or "PH" denotes phenyl.

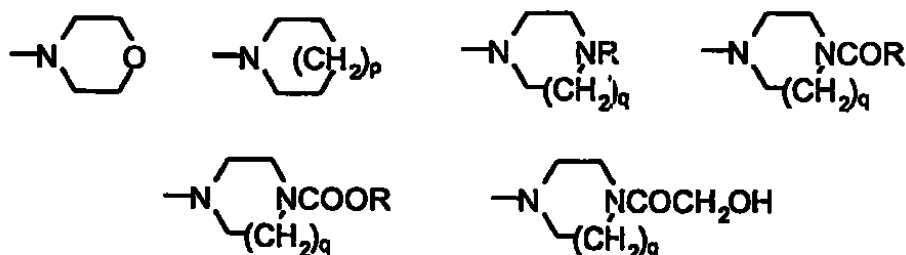
30 Whenever the term "alkyl", "acyl", or "aryl" or either of their prefix roots appear in a name of a substituent (e.g., aralkyl, dialkylamino) it shall be interpreted as including those limitations given above for "alkyl", "acyl", and "aryl." Designated numbers of carbon atoms (e.g., C₁₋₈) shall refer independently to the number of carbon atoms in an alkyl or cycloalkyl moiety or to the alkyl portion of a larger substituent in which alkyl appears as its prefix root.

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Whether used alone or as part of a substituent group, "heteroaryl" refers to a cyclic aromatic radical having from five to ten ring atoms of which one ring atom is selected from S, O, and N; 0-2 ring atoms are additional heteroatoms

independently selected from S, O, and N; and the remaining ring atoms are carbon. The radical being joined to the rest of the molecule via any of the ring atoms, for example, pyridinyl, pyrazinyl, pyrimidinyl, pyrrolyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl, isoxazolyl, thiadiazolyl, triazolyl, oxadiazolyl, thienyl, furanyl, quinolinyl, isoquinolinyl, and the like. The heteroaryl group may be substituted by independent replacement of 1 to 3 of the hydrogen atoms thereon with halogen, -OH, -CN, mercapto, nitro, amino, substituted amino, alkyl, -O-alkyl, -S-alkyl, -NH-alkyl, -N(alkyl)₂, (mono-, di-, tri-, and per-)halo-alkyl, formyl, -COR_s, -COOR_s, -CONHR_s, -CONR_sR_s, -SOR_s, -SO₂R_s, -SO₂NHR_s, -SO₂NR_sR_s, alkyl-COO, alkyl-CONH, or carboxamide, wherein R_s and R_s are defined as hereinabove. Heteroaryl may also be substituted with a mono-oxo to give 4-oxo-1H-quinoline and the like.

A "cyclic amino" derivative is a 4 to 8 membered nitrogen containing cyclic group where the other remaining members are selected from carbon, nitrogen, oxygen or sulfur, for instance an azetidiny group, pyrrolidiny group, piperidiny group, morpholino group, piperaziny, or groups of the following formulae:



wherein p is -2 to 4 and q is 1-4.

"Heterocyclyl" or "heterocycle" is a 3- to 8-member saturated or partially saturated single or fused ring system which consists of carbon atoms and from one to three heteroatoms selected from N, O and S. The heterocyclyl group may be attached at any heteroatom or carbon atom, which results in the creation of a

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stable structure. Examples of heterocyclyl groups include, but are not limited to pyridine, pyrimidine, oxazoline, pyrrole, imidazole, morpholine, furan, indole, benzofuran, pyrazole, pyrrolidine, piperidine, and benzimidazole. "Heterocyclyl" or "heterocycle" may be substituted with one or more independent groups including, but not limited to, H, halogen, oxo, OH, alkyl, substituted alkyl, amino, substituted amino, carboxyl, alkylcarboxyl, and alkoxy.

Unless specified otherwise, it is intended that the definition of any substituent or variable at a particular location in a molecule be independent of its definitions elsewhere in that molecule. It is understood that substituents and substitution patterns on the compounds of this invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art as well as those methods set forth herein.

The compounds of the instant invention are asymmetric in the oxazolidinone ring at the 5- position and thus exist as optical antipodes. As such, all possible optical antipodes, enantiomers or diastereomers resulting from additional asymmetric centers that may exist in optical antipodes, racemates and racemic mixtures thereof are also part of this invention. The antipodes can be separated by methods known to those skilled in the art such as, for example, fractional recrystallization of diastereomeric salts of enantiomerically pure acids. Alternatively, the antipodes can be separated by chromatography on a Pirkle column.

The phrase "a pharmaceutically acceptable salt" denotes salts of the free base which possess the desired pharmacological activity of the free base and which are neither biologically nor otherwise undesirable. These salts may be derived from inorganic or organic acids. Examples of inorganic acids are hydrochloric acid, nitric acid, hydrobromic acid, sulfuric acid, or phosphoric acid. Examples of organic acids are acetic acid, propionic acid, glycolic acid, lactic acid, pyruvic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid,

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methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, methyl sulfonic acid, salicylic acid and the like. Suitable salts are furthermore those of inorganic or organic bases, such as KOH, NaOH, $\text{Ca}(\text{OH})_2$, $\text{Al}(\text{OH})_3$, piperidine, morpholine, ethylamine, triethylamine and the like.

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Also included within the scope of the invention are the hydrated forms of the compounds which contain various amounts of water, for instance, the hydrate, hemihydrate and sesquihydrate forms.

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The term "subject" includes, without limitation, any animal or artificially modified animal. As a particular embodiment, the subject is a human.

The term "drug-resistant" or "drug-resistance" refers to the characteristics of a microbe to survive in presence of a currently available antimicrobial agent such as an antibiotic at its routine, effective concentration.

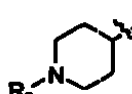
The compounds described in the present invention possess antibacterial activity due to their novel structure, and are useful as antibacterial agents for the treatment of bacterial infections in humans and animals.

In particular, compounds of Formula I wherein X is CH are embodiments of the present invention for such purposes.

Compounds of Formula I wherein R_2 is $\text{C}(\text{O})\text{R}_6$ wherein R_6 is as described above are particular embodiments of this invention.

More particularly, compounds of Formula I wherein R_6 is H or alkyl are also embodiments of this invention.

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Compounds of Formula I wherein R_1 is  or  wherein R_3 is as described above are further particular embodiments of this invention.

More particularly, compounds of Formula I wherein R_{2a} is H and R_3 is selected from $-COR_4$, $-SO_2R_5$ and $(CH_2)_t$ heteroaryl wherein R_4 , R_5 and t are as described above are embodiments of this invention.

5 Still more particularly, compounds of Formula I wherein R_4 is selected from OR_5 , $-(CH_2)_tOR_5$, alkyl, $-(CH_2)_t$ aryl, and $-(CH_2)_t$ heteroaryl wherein R_5 and t are as described above are embodiments of this invention.

10 The following are yet other particular embodiments of the present invention for such purposes:

(S)-N-[[3-[3-fluoro-4-{N-(benzyloxyacetyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-N-[[3-[3-fluoro-4-{N-(α -hydroxyacetyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-N-[[3-[3-fluoro-4-{N-(methanesulfonyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-N-[[3-[3-fluoro-4-{N-(methoxycarbonyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-N-[[3-[3-fluoro-4-{N-(2-pyrimidinyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-N-[[3-[3-fluoro-4-{N-(3-cyanobenzoyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-N-[[3-[3-fluoro-4-{N-(5-cyano-2-pyridyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

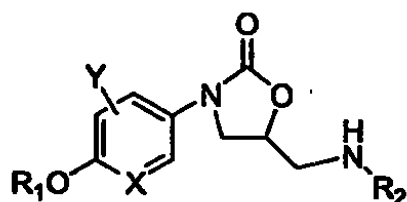
(S)-N-[[3-[3-fluoro-4-{N-(2-thienylcarbonyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-N-[[3-[3-fluoro-4-{N-(α -hydroxyacetyl)piperidinyl-3-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide; and

30 (S)-N-[[3-[3-Fluoro-4-{N-(benzyloxyacetyl)pyrrolidinyl-3-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

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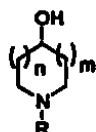
Finally, this invention provides a process for preparing a compound of Formula Ia



Formula Ia

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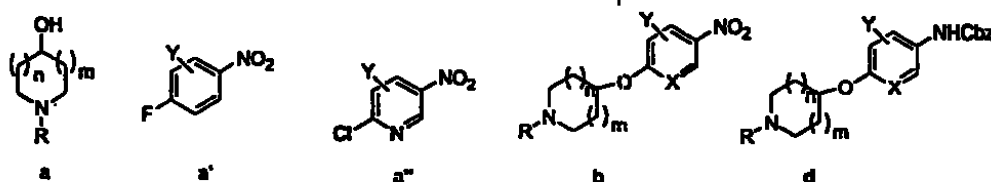
wherein R₁ is a moiety of the formula:



• wherein:

R is selected from Boc, -CH(Ph)₂ or -COCH₂OCH₂Ph, n is 0, 1 or 2, m is 0 or 1, and R₂, X, and Y are as described above, which process comprises:

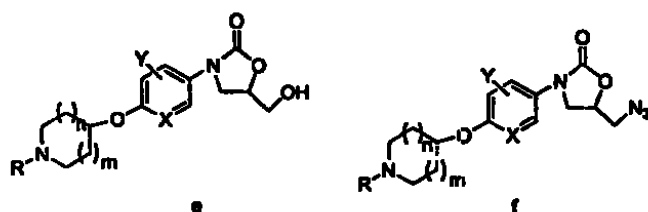
(a) reacting a compound of Formula a with a compound of Formula a' or a'' to form a compound of Formula b;



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(b) converting the compound of Formula b to a compound of Formula d;

(c) reacting the compound of Formula d with to form a compound of Formula e;

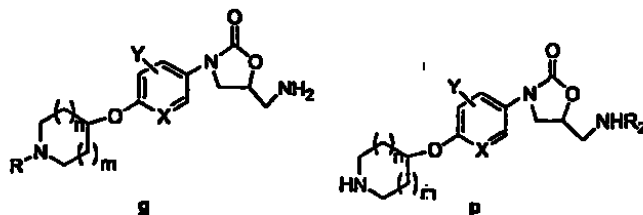


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(d) converting the compound of Formula e to a compound of Formula f;

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(e) converting the compound of Formula f to a compound of Formula g;



5 (f) converting the compound of Formula g to a compound of Formula p; and

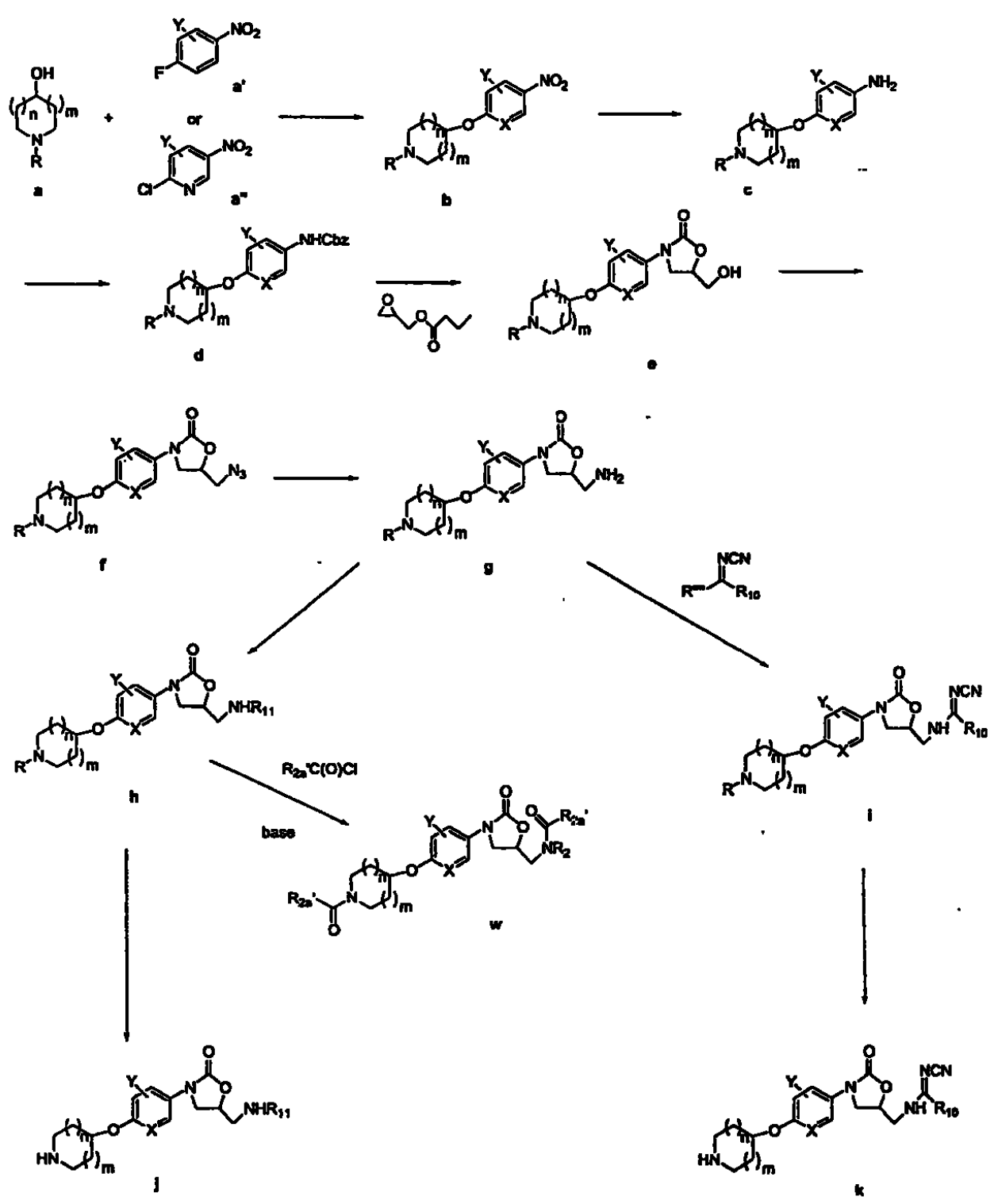
(g) converting the compound of Formula p to a compound of Formula Ia.

The compounds of Formula I may be prepared from readily available starting materials such as known oxazolidinone intermediates in accordance with synthetic methods well known in the art. The following are representative procedures outlined in Schemes I and II:

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Scheme I

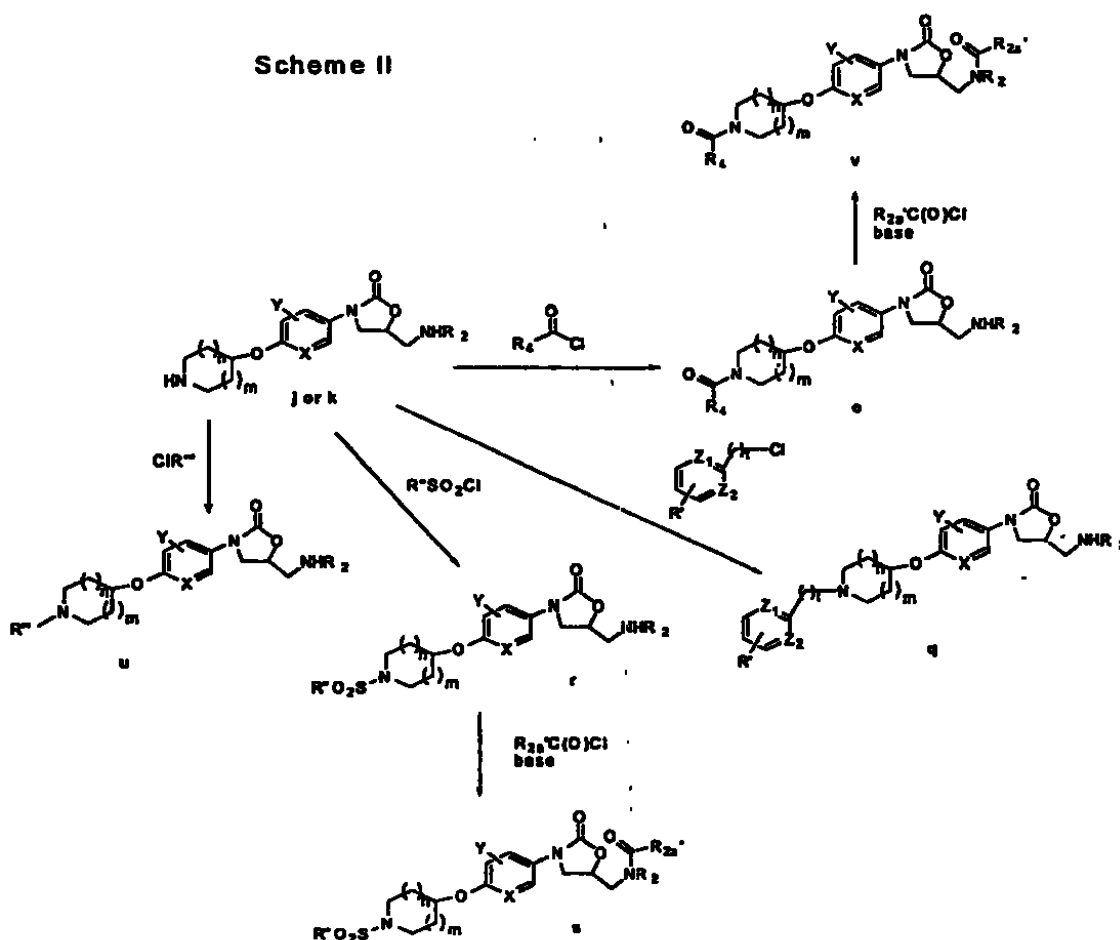
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In accordance with Scheme 1, wherein R is Boc, -CH(Ph)₂ or -COCH₂OCH₂Ph, R₁₁ is -COR₉ or -CO₂R₉, R' is any of the substituents on an aryl or heteroaryl group as described above, R'' is selected from R₉ and -NR₅R₉, R''' is selected from alkyl, substituted alkyl and -CHR₅R₉, R_{2a}' is optionally substituted alkyl, R''' is -SCH₃ or -OCH₃, R₁₀ is -NR₉R₉, R₉, -SR₉, or -NHR₉, n is 0, 1 or 2 and m is 0 or 1, and X, Y, R₄, R₅, R₆, R₉, and t are as described above, an appropriately substituted halo-nitrobenzene such as that of Formula a' or an appropriately substituted halo-nitropyridine such as that of Formula a'' is added to a compound of Formula a (all of which are either commercially available or may be readily prepared by known methods) in acetone, dimethylformamide (DMF), or tetrahydrofuran (THF). The mixture is treated with an appropriate base such as potassium t-butoxide (KOtBu) to obtain the corresponding compound of Formula b. The compound of Formula b may be reduced to the corresponding compound of Formula c under appropriate conditions such as H₂, Pd/C and ethanol (EtOH) or NH₄OCOH, Pd/C and methanol (MeOH). Then compound c is treated with benzylchloroformate (CbzCl) in the presence of an appropriate base such as cesium carbonate (CsCO₃) in an appropriate solvent such as THF, H₂O or acetone to obtain the corresponding compound of Formula d. Compound d is then treated with an appropriate base such as nBuLi, followed by addition of glycidyl butyrate in an appropriate solvent such as THF to obtain the corresponding compound of Formula e. The compound of Formula e is treated with methanesulfonyl chloride (MsCl) and an appropriate base such as triethylamine (NEt₃) in an appropriate solvent such as methylene chloride (CH₂Cl₂). After standard workup, sodium azide (NaN₃) is then added into the mixture in an appropriate solvent such as dimethylformamide (DMF) and heated at a preferred temperature range of 70°C to 90°C to obtain the corresponding compound of Formula f. The compound of Formula f may be reduced under appropriate conditions such as H₂ and Pd/C in an appropriate solvent such as ethyl acetate (EtOAc), or the compound of Formula f may be reduced using triphenylphosphine (PPh₃) and THF/H₂O to obtain the corresponding compound of Formula g.

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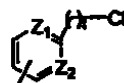
The compound of Formula g can be treated with an appropriate acylating agent such as acetic anhydride (Ac_2O) or acetyl chloride (AcCl), along with an appropriate base such as pyridine or NEt_3 to give the corresponding compound of Formula h. The compound of Formula g can also be treated with an appropriate imidate to give the corresponding compound of Formula i. Compound h wherein R is $-\text{CH}(\text{Ph})_2$ can be converted to the corresponding compound of Formula w by reacting with $\text{R}_{2\text{a}}'\text{C}(\text{O})\text{Cl}$ in the presence of a base such as TEA. Compounds j and k can be obtained from compounds h and i, respectively, by deprotection with either trifluoroacetic acid (TFA) in an appropriate solvent such as CH_2Cl_2 or with Pd/C in an appropriate solvent such as EtOH or EtOAc.

Compounds of Formulae o, q, r, s, and u may be obtained in accordance with different routes as shown in Scheme II:



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The compound of Formula j or k can be treated with an appropriate alkylating agent represented by ClR^m in the presence of an appropriate base such as NEt_3 in an appropriate solvent such as CH_2Cl_2 or THF to obtain the corresponding compound of Formula u. Alternatively, the compound of Formula j or k can be treated with an appropriate sulfonyl chloride represented by $\text{R}^n\text{SO}_2\text{Cl}$ such as MsCl in the presence of an appropriate base such as NEt_3 in an appropriate solvent such as CH_2Cl_2 or THF to obtain the corresponding compound of Formula r. Still alternatively, the compound of Formula j or k can be treated



with an appropriate alkylating agent represented by R^m , wherein Z_1 and Z_2 are independently N or CH, in the presence of an appropriate base such as NEt_3 in an appropriate solvent such as CH_2Cl_2 or THF to obtain the corresponding compound of Formula q. In addition, the compound of Formula j or k can also be treated with an appropriate acylating agent represented by R_4COCl such as AcCl in the presence of an appropriate base such as NEt_3 in an appropriate solvent such as CH_2Cl_2 or THF to obtain the corresponding compound of Formula o. In several cases, R_4 contains a protected amine or protected alcohols moiety. After removal of the protecting group, the resulting amine or alcohol can be further derivatized. Compounds of Formulae o and r can be converted to compounds of Formulae v and s, respectively, by reacting with $\text{R}_2\text{C}(\text{O})\text{Cl}$ in the presence of a base such as TEA.

These compounds have antimicrobial activity against susceptible and drug resistant *S. aureus*, *S. epidermidis*, *S. pneumoniae*, *E. faecalis*, *E. faecium*, *Moraxella catarrhalis* and *H. influenzae*. These compounds are particularly useful against drug resistant Gram positive cocci such as methicillin-resistant staphylococci and vancomycin-resistant enterococci. These compounds are useful in the treatment of community-acquired pneumonia, upper and lower respiratory tract infections, skin and soft tissue infections, hospital-acquired lung infections, bone and joint infections, and other bacterial infections.

Minimal inhibitory concentration (MIC) has been an indicator of in vitro antibacterial activity widely used in the art. The in vitro antimicrobial activity of the

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compounds was determined by the microdilution broth method following the test method from the National Committee for Laboratory Standards (NCCLS). This method is described in the NCCLS Document M7-A4, Vol.17, No.2, "Methods for Dilution Antimicrobial Susceptibility Test for Bacteria that Grow Aerobically—Fourth Edition", which is incorporated herein by reference.

In this method two-fold serial dilutions of drug in cation adjusted Mueller-Hinton broth are added to wells in microdilution trays. The test organisms are prepared by adjusting the turbidity of actively growing broth cultures so that the final concentration of test organism after it is added to the wells is approximately 5×10^4 CFU/well.

Following inoculation of the microdilution trays, the trays are incubated at 35 °C for 16-20 hours and then read. The MIC is the lowest concentration of test compound that completely inhibits growth of the test organism. The amount of growth in the wells containing the test compound is compared with the amount of growth in the growth-control wells (no test compound) used in each tray. As set forth in Table 1, compounds of the present invention were tested against a variety of Gram positive and Gram negative pathogenic bacteria resulting in a range of activities, from 1 to ≥ 128 $\mu\text{g/mL}$ depending on the organism tested.

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Table 1. MIC Values of Some Compounds of Formula I

Com- pound No.	MIC (µg/mL)			Com- pound No.	MIC (µg/mL)		
	<i>E. faecium</i> OC3312	MRSA OC 2878	<i>S. aureus</i> Broth		<i>E. faecium</i> OC3312	MRSA OC 2878	<i>S. aureus</i> Broth
1	>32	16	32	32	32	8	16
2	8	32	8	33	32	16	16
3	4	2	4	34	>128	64	128
4	8	4	4	35	64	32	32
5	16	8	8	36	16	8	8
6	8	4	4	37	16	8	8
7	16	8	8	38	32	8	16
8	8	4	8	39	16	16	16
9	8	4	4	40	16	8	4
10	32	16	16	41	>128	64	128
11	16	8	16	42	>128	32	32
12	16	8	8	43	>128	128	128
13	16	8	8	44	128	64	32
14	8	4	4	45	128	64	64
15	8	8	8	46	>128	64	64
16	32	32	32	47	>128	64	64
17	16	16	8	48	>128	32	64
18	64	16	8	49	>128	128	> 64
19	32	32	16	50	>64	64	>64
20	16	8	8	51	8	8	16
21	64	32	32	52	4	8	8
22	8	4	8	53	16	8	8
23	16	4	16	54	8	8	8
24	32	16	8	55	8	16	16
25	64	32	32	56	32	32	32
26	16	8	16	57	16	16	16
27	16	16	16	58	4	4	8
28	16	8	16	59	16	8	4
29	32	16	32	60	>128	16	8
30	16	8	16	61	128	64	32
31	32	16	16				

5 This invention further provides a method of treating bacterial infections, or enhancing or potentiating the activity of other antibacterial agents, in warm-blooded animals, which comprises administering to the animals a compound of the invention alone or in admixture with another antibacterial agent in the form of a medicament according to the invention.

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When the compounds are employed for the above utility, they may be combined with one or more pharmaceutically acceptable carriers, e.g., solvents, diluents, and the like, and may be administered orally in such forms as tablets, capsules, dispersible powders, granules, or suspensions containing for example, from about 0.5% to 5% of suspending agent, syrups containing, for example, from about 10% to 50% of sugar, and elixirs containing, for example, from about 20% to 50% ethanol, and the like, or parenterally in the form of sterile injectable solutions or suspensions containing from about 0.5% to 5% suspending agent in an isotonic medium. These pharmaceutical preparations may contain, for example, from about 0.5% up to about 90% of the active ingredient in combination with the carrier, more usually between 5% and 60% by weight.

Compositions for topical application may take the form of liquids, creams or gels, containing a therapeutically effective concentration of a compound of the invention admixed with a dermatologically acceptable carrier.

In preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed. Solid carriers include starch, lactose, dicalcium phosphate, microcrystalline cellulose, sucrose and kaolin, while liquid carriers include sterile water, polyethylene glycols, non-ionic surfactants and edible oils such as corn, peanut and sesame oils, as are appropriate to the nature of the active ingredient and the particular form of administration desired.

Adjuvants customarily employed in the preparation of pharmaceutical compositions may be advantageously included, such as flavoring agents, coloring agents, preserving agents, and antioxidants, for example, vitamin E, ascorbic acid, BHT and BHA.

The preferred pharmaceutical compositions from the standpoint of ease of preparation and administration are solid compositions, particularly tablets and hard-filled or liquid-filled capsules. Oral administration of the compounds is preferred. These active compounds may also be administered parenterally or intraperitoneally. Solutions or suspensions of these active compounds as a free base or pharmacological acceptable salt can be prepared in water suitably mixed

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with a surfactant such as hydroxypropyl-cellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations may contain a preservative to prevent the growth of microorganisms.

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The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils.

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The effective dosage of active ingredient employed may vary depending on the particular compound employed, the mode of administration and the severity of the condition being treated. However, in general, satisfactory results are obtained when the compounds of the invention are administered at a daily dosage of from about 0.1 mg/kg to about 400 mg/kg of animal body weight, preferably given in divided doses two to four times a day, or in sustained release form. For most large mammals the total daily dosage is from about 0.07 g to 7.0 g, preferably from about 100 mg to 1000 mg. Dosage forms suitable for internal use comprise from about 100 mg to 500 mg of the active compound in intimate admixture with a solid or liquid pharmaceutically acceptable carrier. This dosage regimen may be adjusted to provide the optimal therapeutic response. For example, several divided doses may be administered daily or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic situation.

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The production of the above-mentioned pharmaceutical compositions and medicaments is carried out by any method known in the art, for example, by mixing the active ingredients(s) with the diluent(s) to form a pharmaceutical

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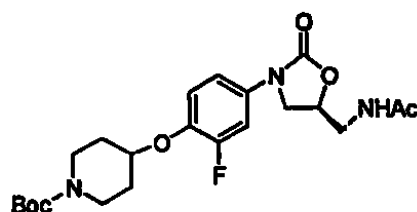
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composition (e.g. a granulate) and then forming the composition into the medicament (e.g. tablets).

The following examples describe in detail the chemical synthesis of representative compounds of the present invention. The procedures are illustrations, and the invention should not be construed as being limited by chemical reactions and conditions they express. No attempt has been made to optimize the yields obtained in these reactions, and it would be obvious to one skilled in the art that variations in reaction times, temperatures, solvents, and/or reagents could increase the yields.

Example 1

(S)-N-[[3-[3-Fluoro-4-{N-(*t*-butoxycarbonyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide



Compound 1

N-(*t*-Butoxycarbonyl)-4-piperidinol:

To a solution of 25 g (247 mmol) 4-piperidinol in 350 mL dry tetrahydrofuran (THF) at 0°C was added dropwise 60.2 g (276 mmol) di-*t*-butylcarbonate in 350 mL dry THF. The reaction was allowed to warm to room temperature (rt) and stirred overnight. The solvent was removed under reduced pressure, the resulting residue dissolved in 700 mL CH₂Cl₂ and the solution extracted with H₂O (1 x 400 mL), dried over MgSO₄, filtered and rotary evaporated to yield 45 g (91%) of N-(*t*-butoxycarbonyl)-4-piperidinol as an oil which slowly solidified to white crystals. ¹H NMR (CDCl₃) δ 3.75-3.96 (m, 3H); 2.92-3.13 (m, 2H); 1.80-1.93 (m, 4H); and 1.48 (s, 9H).

1-[N-(*t*-Butoxycarbonyl)piperidinyl-4-oxy]-2-fluoro-4-nitrobenzene:

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To a solution of 740 mg (3.7 mmol) of N-(t-butoxycarbonyl)-4-piperidinol in 10 mL dry THF at 0°C was added dropwise 4 mL (4.0 mmol) 1M KOtBu. After stirring at 0°C for 0.5 h, 0.40 mL (3.6 mmol) 3,4-difluoronitrobenzene was added and the reaction warmed to rt and stirred overnight. The reaction was poured into 100 mL H₂O and extracted with CH₂Cl₂ (3 x 100 mL). The combined aqueous layers were washed with H₂O, dried with MgSO₄, filtered, and the solvent removed by rotary evaporation. Then the solid was triturated with cold hexanes to afford 1.1 g (89%) of 1-[N-(t-butoxycarbonyl)piperidinyl-4-oxy]-2-fluoro-4-nitrobenzene as a pale yellow solid; mp 88-90°C, MS (CI) [M+Na]⁺ 364.

1-[4-(N-t-Butoxycarbonyl)piperidinyl-4-oxy]-2-fluoro-4-aminobenzene:

To 1.78 g (5.23 mmol) of 1-[N-(t-butoxycarbonyl)piperidinyl-4-oxy]-2-fluoro-4-nitrobenzene in 100 mL MeOH was added 1.05 g (16.6 mmol) ammonium formate and 70 mg 10% Pd/C and the reaction heated at reflux under N₂ for 2 h. The reaction was filtered through a pad of celite and the filtrate evaporated to afford crude aniline as a gold oil. The material was used without further purification in the next step.

2-Fluoro-1-[N-(t-butoxycarbonyl)piperidinyl-4-oxy]-4-(phenylmethoxycarbonylamino)benzene:

To 1-[4-(N-t-butoxycarbonyl)piperidinyl-4-oxy]-2-fluoro-4-aminobenzene (5.23 mmol) in 150 mL 2:1 acetone:H₂O at 0°C was added 1.03 g (12.3 mmol) NaHCO₃ and 0.90 mL (6.30 mmol) benzylchloroformate. After stirring at rt for 6 h the volatiles were evaporated, the residue diluted with 300 mL H₂O and extracted with Et₂O (3 x 150 mL). The combined organic layers were washed with H₂O, dried over MgSO₄, filtered, and the solvent removed by rotary evaporation. Silica gel chromatography (20% EtOAc in Hexanes) afforded 2.06 g (89%) of 2-fluoro-1-[N-(t-butoxycarbonyl)piperidinyl-4-oxy]-4-(phenylmethoxycarbonylamino)benzene as a yellow, waxy solid. ¹H NMR (CDCl₃) δ 7.3-7.4 (m, 6H); 6.9-7.0 (m, 2H); 6.60 (brs, 1H); 4.3-4.4 (m, 1H); 3.7-3.8 (m, 2H); 3.2-3.3 (m, 2H); 1.8-2.0 (m, 2H); 1.6-1.8 (m, 2H); and 1.48 (s, 9H).



(R)-[3-[3-Fluoro-4-(N-(t-butoxycarbonyl)piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methanol:

To 1.73 g (3.89 mmol) of 2-fluoro-1-{N-(t-butoxycarbonyl)piperidinyl-4-oxy}-4-(phenylmethoxycarbonylamino)benzene in 25 mL dry THF at -78 °C was added 2 mL (5.0 mmol) 2.5M *n*-BuLi and the reaction stirred for 1 h. Then 0.71 mL (5.01 mmol) (R)-glycidyl butyrate was added via syringe and the reaction warmed to rt and stirred overnight. The reaction was carefully poured into 150 mL sat. NH₄Cl (aq.) and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with H₂O, dried over MgSO₄, filtered, and the solvent removed by rotary evaporation. Silica gel chromatography (40% EtOAc in hexanes to 70% EtOAc in hexanes) gave 1.15 g (72%) of (R)-[3-[3-fluoro-4-(N-(t-butoxycarbonyl)piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methanol as a white solid; mp 110-111°C, MS (CI) [M+Na]⁺ 433.5.

(R)-[3-[3-Fluoro-4-(N-(t-butoxycarbonyl)piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl methanesulfonate:

To 1.03 g (2.51 mmol) of (R)-[3-[3-fluoro-4-(N-(t-butoxycarbonyl)piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methanol in 50 mL CH₂Cl₂ at 0°C was added 0.70 mL (5.02 mmol) NEt₃ and 0.37 mL (4.78 mmol) methanesulfonyl chloride. After stirring for 3 h at 0°C the reaction was poured into 75 mL H₂O and extracted with CH₂Cl₂ (100 mL). The combined organic layers were washed with H₂O, dried over MgSO₄, filtered and the solvent removed by rotary evaporation to yield 1.21 g (99%) of (R)-[3-[3-fluoro-4-(N-(t-butoxycarbonyl)piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl methanesulfonate as a cream solid; mp 127-129°C, MS (CI) [M+H-Boc]⁺ 389.2.

(R)-[3-[3-Fluoro-4-(N-(t-butoxycarbonyl)piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methylazide:

To a solution of (R)-[3-[3-fluoro-4-(N-(t-butoxycarbonyl)piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl methanesulfonate (5.20 mmol) in 70 mL dimethylformamide (DMF) was added 1.22 g (18.8 mmol) sodium azide and the reaction heated at 75°C overnight. Then the reaction was poured into 300 mL H₂O and extracted with EtOAc (3 x 200 mL). The combined organic layers were

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washed with H₂O (3 x 200 mL), dried over MgSO₄, filtered, and the solvent removed by rotary evaporation to yield 2.07 g (92%) of (R)-[3-[3-fluoro-4-(N-(t-butoxycarbonyl)piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methylazide as a beige solid. ¹H NMR (CDCl₃) δ 7.46 (dd, J = 12.9 and 2.7 Hz, 1H); 7.14 (dt, J = 8.9 and 1.4 Hz, 1H); 7.01 (t, J = 8.9 Hz, 1H); 4.7-4.8 (m, 1H); 4.3-4.4 (m, 1H); 4.05 (t, J = 8.9 Hz, 1H); 3.83 (dd, J = 8.9 and 6.2 Hz, 1H); 3.7-3.8 (m, 2H); 3.71 (dd, J = 13.2 and 4.6 Hz, 1H); 3.59 (dd, J = 13.2 and 4.3 Hz, 1H); 3.2-3.3 (m, 2H); 1.8-2.0 (m, 2H); 1.7-1.8 (m, 2H); and 1.47 (s, 9H).

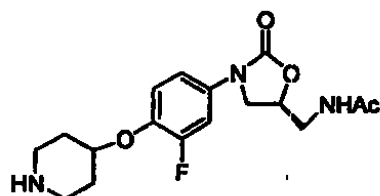
10 (S)-N-[[3-[3-Fluoro-4-(N-(t-butoxycarbonyl)piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (Compound 1):

To a solution of (R)-[3-[3-fluoro-4-(N-(t-butoxycarbonyl)piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methylazide (5.20 mmol) in 9 mL dry THF was added 1.51 g (5.75 mmol) triphenylphosphine and the reaction stirred for 3 h at rt. Then 4.5 mL H₂O was added and the reaction heated at 60°C for 4 h. The volatiles were evaporated and the residue azeotroped with benzene (2 x 20 mL) to yield the crude amine.

To a solution of this crude amine in 100 mL EtOAc was added 0.58 mL (6.15 mmol) acetic anhydride and 1.2 mL (14.8 mmol) pyridine, and the reaction stirred at rt overnight. The reaction mixture was poured into 250 mL H₂O, extracted with EtOAc, dried over MgSO₄, filtered, and the solvent removed under reduced pressure. Silica gel chromatography (100% EtOAc to 5% MeOH in EtOAc) yielded 1.85 g (79%) of (S)-N-[[3-[3-fluoro-4-(N-(t-butoxycarbonyl)piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide as a white solid; mp 179-180°C, MS (CI) [M+Na]⁺ 474.

Example 2

(S)-N-[[3-[3-Fluoro-4-(piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide



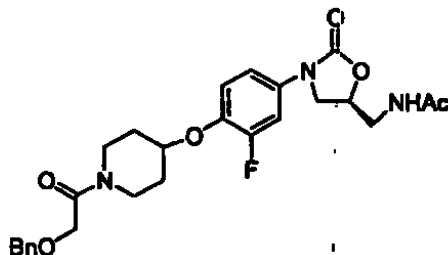
235

Compound 2

To a solution of 1.94 g (4.30 mmol) of Compound 1 in 225 mL CH₂Cl₂ was added 2.5 mL (32.5 mmol) trifluoroacetic acid (TFA) and the reaction stirred at rt for 6 h. The volatiles were evaporated under reduced pressure. The resulting oil (TFA salt) was dissolved in 100 mL H₂O, extracted with EtOAc (100 mL), and the aqueous layer was cooled to 0°C and basicified with 1N NaOH. This solution was extracted with EtOAc (5 x 200 mL), the combined extracts washed with brine, dried over MgSO₄, filtered, and evaporated under reduced pressure to yield (S)-N-[[3-[3-fluoro-4-{piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide as a pale yellow glass; mp 55-59°C, MS (CI) [M+H]⁺ 352.

Example 3

(S)-N-[[3-[3-Fluoro-4-{N-(benzyloxyacetyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

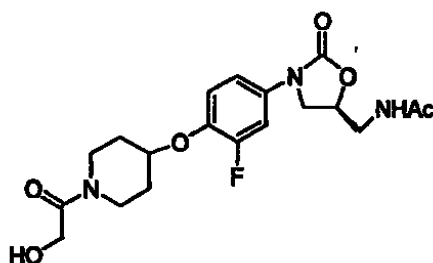


Compound 3

To a suspension of Compound 2 (1.50 mmol) in 50 mL CH₂Cl₂ was added 0.60 mL (4.3 mmol) NEt₃ and 0.25 mL (1.58 mmol) benzyloxyacetyl chloride. After stirring for 18 h, the reaction was poured into 75 mL H₂O and extracted with CH₂Cl₂ (4 x 50 mL). The combined organic layers were dried over MgSO₄, filtered, and evaporated under reduced pressure. Silica gel chromatography (5% MeOH in EtOAc) afforded (S)-N-[[3-[3-fluoro-4-{N-(benzyloxyacetyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl] acetamide as a white glass. ¹H NMR (CDCl₃) δ 7.47 (dd, J = 12.9 and 2.5 Hz, 1H); 7.2-7.4 (m, 6H); 6.98 (t, J = 8.8 Hz, 1H); 6.24 (brt, J = 6.1 Hz, 1H); 4.7-4.8 (m, 1H); 4.61 (s, 2H); 4.4-4.5 (m, 1H); 4.20 (s, 2H); 4.02 (t, J = 9.0 Hz, 1H); 3.6-3.8 (m, 6H); 3.4-3.5 (m, 1H); 2.02 (s, 3H); and 1.8-1.9 (m, 4H).

Example 4

(S)-N-[[3-[3-Fluoro-4-{N-(α -hydroxyacetyl)piperidinyl-4-oxy}phenyl]-
2-oxo-5-oxazolidinyl]methyl]acetamide

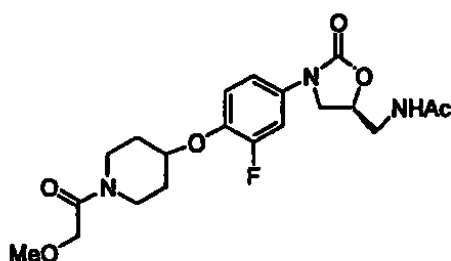


Compound 4

To a solution of 540 mg (1.08 mmol) of Compound 3 in 50 mL MeOH was added 503 mg ammonium formate and a catalytic amount of 10% Pd/C, and the reaction was heated at reflux overnight. Then the reaction was filtered through a pad of celite and the solvent removed under reduced pressure. Silica gel chromatography (2% to 10% MeOH in CH₂Cl₂) afforded (S)-N-[[3-[3-fluoro-4-{N-(α -hydroxyacetamide)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide as a hygroscopic white foam (93%). ¹H NMR (CDCl₃) δ 7.49 (dd, J = 12.9 and 2.6 Hz, 1H); 7.09 (dd, J = 8.9 and 1.6 Hz, 1H); 7.00 (t, J = 8.9 Hz, 1H); 6.18 (brt, J = 6.1 Hz, 1H); 4.7-4.8 (m, 1H); 4.51 (q, J = 4.6 Hz, 1H); 4.19 (s, 2H); 4.02 (t, J = 9.0 Hz, 1H); 3.5-3.8 (m, 7H); 3.20 (dt, J = 13.7 and 5.2 Hz, 1H); 2.03 (s, 3H); and 1.90 (m, 4H).

Example 5

(S)-N-[[3-[3-Fluoro-4-{N-(methoxyacetyl)piperidinyl-4-oxy}phenyl]-
2-oxo-5-oxazolidinyl]methyl]acetamide

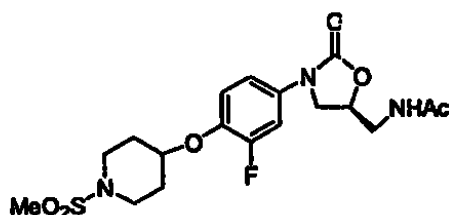


Compound 5

To a solution of (S)-N-[[3-[3-fluoro-4-(piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (0.756 mmol) in 30 mL EtOAc was added 1.0 mL (7.17 mmol) NEt₃ and methoxyacetylchloride (0.875 mmol). The reaction stirred at rt for 2.5 h, was poured into 50 mL H₂O, and extracted with EtOAc. The organic layer was washed with H₂O, dried over MgSO₄, filtered, and the solvent removed by rotary evaporation to yield the impure amide. Silica gel chromatography (2.5 to 10% MeOH in CH₂Cl₂) afforded 101 mg (32%) of (S)-N-[[3-[3-fluoro-4-(N-(methoxyacetyl) piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide as a beige foam. ¹H NMR (CDCl₃) δ 7.48 (dd, J = 12.9 and 2.5 Hz, 1H); 7.10 (m, 1H); 7.00 (t, J = 8.8 Hz, 1H); 6.00 (brt, 1H); 4.77 (m, 1H); 4.46 (m, 1H); 4.13 (s, 2H); 4.03 (t, J = 8.9 Hz, 1H); 3.5-3.8 (m, 6H); 3.44 (s, 3H); 3.43 (m, 1H); 2.03 (s, 3H); and 1.7-1.9 (m, 4H).

Example 6

(S)-N-[[3-[3-Fluoro-4-(N-(methanesulfonyl)piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide



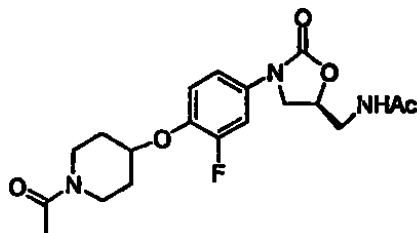
Compound 6

To a solution of 115 mg (0.33 mmol) of Compound 2 in 5 mL CH₂Cl₂ was added 0.05 mL (0.36 mmol) NEt₃ and 0.03 mL (0.39 mmol) methanesulfonyl chloride. The reaction stirred at rt for 22 h, was poured into 50 mL H₂O, and extracted with CH₂Cl₂. The combined organic layers were washed with H₂O, dried over MgSO₄, filtered, and the solvent removed by rotary evaporation to yield the impure sulfonamide. The sulfonamide was purified by dissolving in EtOAc, washing with sat. NaHCO₃, drying over MgSO₄, and removal of the solvent under reduced pressure to give (S)-N-[[3-[3-fluoro-4-(N-(methanesulfonyl)piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl] acetamide; mp 123-125°C, MS (CI) [M+H]⁺ 430.

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240

Example 7

(S)-N-[[3-[3-Fluoro-4-{N-(acetyl)piperidiny-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

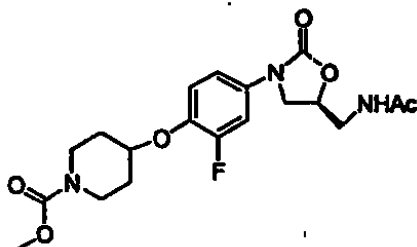


Compound 7

To a solution of 155 mg (0.44 mmol) of Compound 2 in 30 mL CH₂Cl₂ was added 0.10 mL (0.72 mmol) NEt₃ and 0.05 mL (0.70 mmol) acetyl chloride. The reaction stirred at rt for 18 h, was poured into 50 mL H₂O, and extracted with CH₂Cl₂. The combined organic layers were washed with H₂O, dried over MgSO₄, filtered, and the solvent removed by rotary evaporation to yield the impure amide. The amide was purified by dissolving in EtOAc, washing with sat. NaHCO₃, drying over MgSO₄, and the solvent removed under reduced pressure to give (S)-N-[[3-[3-fluoro-4-{N-(acetyl)piperidiny-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide. ¹H NMR (CDCl₃) δ 7.47 (dd, J = 12.9 and 2.2 Hz, 1H); 7.06 (m, 2H); 6.97 (brt, J = 8.8 Hz, 1H); 4.79 (m, 1H); 4.46 (m, 1H); 4.03 (t, J = 9.0 Hz, 1H); 3.6-3.8 (m, 6H); 3.52 (m, 1H); 2.12 (s, 3H); 2.02 (s, 3H); and 1.88 (m, 4H).

Example 8

(S)-N-[[3-[3-Fluoro-4-{N-(methoxycarbonyl)piperidiny-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide



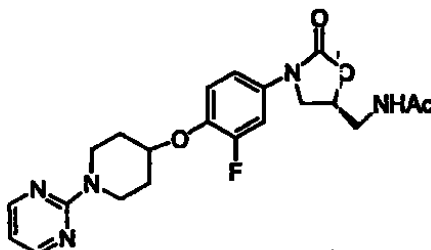
Compound 8

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To a solution of 201 mg (0.57 mmol) of Compound 2 in 50 mL EtOAc was added 0.15 mL NEt₃ and 0.10 mL methylchloroformate. The reaction stirred at rt for 20 h, was poured into 50 mL H₂O, and extracted with EtOAc. The combined organic layers were washed with H₂O, dried over MgSO₄, filtered, and the solvent removed by rotary evaporation to yield 167 mg (72%) of (S)-N-[[3-[3-fluoro-4-(N-(methoxycarbonyl)piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide as a white solid. ¹H NMR (CDCl₃) δ 7.47 (m, 1H); 7.26 (m, 1H); 7.06 (m, 1H); 6.03 (m, 1H); 4.78 (m, 1H); 4.41 (m, 1H); 4.02 (t, J = 8.9 Hz, 1H); 3.71 (s, 3H); 3.6-3.7 (m, 5H); 3.41 (m, 2H); 2.02 (s, 3H); 1.89 (m, 2H); and 1.79 (m, 2H).

Example 9

(S)-N-[[3-[3-Fluoro-4-(N-(2-pyrimidinyl)piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

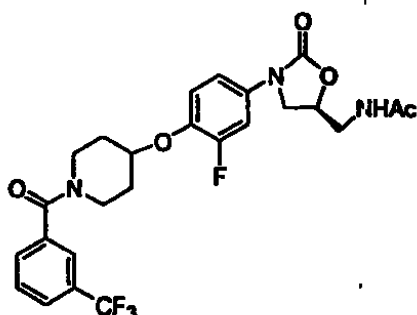


Compound 9

To a solution of 176 mg (0.50 mmol) of Compound 2 in 7.5 mL EtOH was added 0.23 mL NEt₃ and 61 mg (0.53 mmol) 2-chloropyrimidine and the reaction heated at reflux for 21 h. After cooling, the reaction was poured into 50 mL sat. NaHCO₃, and extracted with CH₂Cl₂ (4 x 50 mL). The combined organic layers were washed with H₂O, dried over MgSO₄, filtered, and the solvent removed by rotary evaporation to yield 174 mg (81%) of (S)-N-[[3-[3-fluoro-4-(N-(2-pyrimidinyl)piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide; mp 121-123°C, MS (CI) [M+H]⁺ 430.

Example 10

(S)-N-[[3-[3-Fluoro-4-(N-(3-trifluoromethylbenzoyl)piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

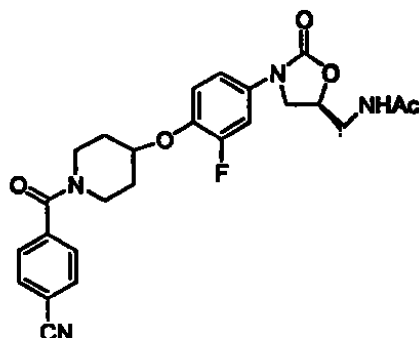


Compound 10

To a solution of 101 mg (0.29 mmol) of Compound 2 in 10 mL CH₂Cl₂ was added 260 mg AMBERLYST 21 Basic Resin and 1.0 mL (6.6 mmol) 3-trifluoromethylbenzoyl chloride and the reaction shaken for 3.5 h at rt. Then 2.4 g P-trisamine was added and the reaction shaken overnight. The reaction was filtered and the resin washed with CH₂Cl₂. The combined organic layers were washed with sat. NaHCO₃, dried over MgSO₄, filtered, and the solvent removed by rotary evaporation to yield the crude amide. The amide was triturated with hexanes 3 times to afford 100 mg (67%) of (S)-N-[[3-[3-fluoro-4-{N-(3-trifluoromethylbenzoyl)piperidin-4-yl}oxy]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide as a white powder; mp 150-152°C, MS (CI) [M+H]⁺ 524.

Example 11

(S)-N-[[3-[3-Fluoro-4-{N-(4-cyanobenzoyl)piperidin-4-yl}oxy]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide



Compound 11

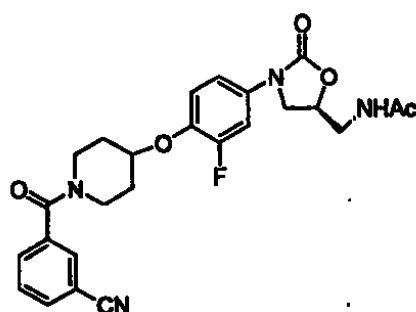
To a solution of 51 mg (0.15 mmol) of Compound 2 in 7.5 mL CH₂Cl₂ was added 207 mg AMBERLYST 21 Basic Resin and 116 mg (0.70 mmol) 4-

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5 cyanobenzoyl chloride and the reaction was shaken for 18 h at rt. Then 250 mg P-trisamine was added and the reaction was shaken for 20 h. The reaction was filtered and the resin washed with CH₂Cl₂. The organic solvent was removed by rotary evaporation to yield 63 mg (91%) of (S)-N-[[3-[3-fluoro-4-{N-(4-cyanobenzoyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl] acetamide; mp 75-78°C, MS (CI) [M+H]⁺ 481.

Example 12

(S)-N-[[3-[3-Fluoro-4-{N-(3-cyanobenzoyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide



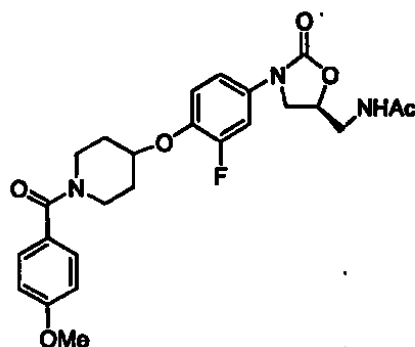
Compound 12

To a solution of 75 mg (0.21 mmol) of Compound 2 in 7.5 mL CH₂Cl₂ was added 200 mg AMBERLYST 21 Basic Resin and 128 mg (0.77 mmol) 3-cyanobenzoyl chloride and the reaction was shaken for 18 h at rt. Then 300 mg P-trisamine was added and the reaction was shaken for 20 h. The reaction was filtered and the resin washed with CH₂Cl₂. The organic solvent was removed by rotary evaporation to yield 103 mg (100%) of (S)-N-[[3-[3-fluoro-4-{N-(3-cyanobenzoyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl] acetamide; mp 82-85°C, MS (CI) [M+H]⁺ 481.

Example 13

(S)-N-[[3-[3-Fluoro-4-{N-(4-methoxybenzoyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

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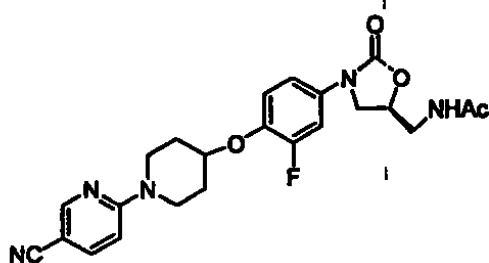


Compound 13

To a solution of 133 mg (0.29 mmol) of Compound 2 in 10 mL CH₂Cl₂ was added 350 mg AMBERLYST 21 Basic Resin and 255 mg (1.49 mmol) *p*-anisoyl chloride and the reaction was shaken for 3 h at rt. Then 1.0 g P-trisamine was added and the reaction was shaken for 48 h. The reaction was filtered and the resin washed with CH₂Cl₂. The organic solvent was removed by rotary evaporation to yield (S)-N-[[3-[3-fluoro-4-(N-(4-methoxybenzoyl) piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide as a yellow glass; ¹H NMR (CDCl₃) δ 7.50 (m, 1H); 7.39 (m, 2H); 7.05 (m, 1H); 7.03 (m, 1H); 6.90 (m, 2H); 6.02 (m, 1H); 4.78 (m, 1H); 4.55 (m, 1H); 4.01 (m, 1H); 3.90 (s, 3H); 3.6-3.9 (m, 7H); 2.06 (s, 3H); and 1.95 (m, 4H).

Example 14

(S)-N-[[3-[3-Fluoro-4-(N-(5-cyano-2-pyridyl)piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide



Compound 14

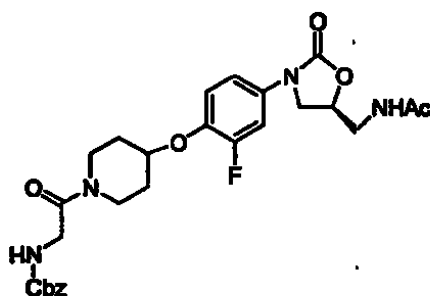
To a solution of 170 mg (0.48 mmol) of Compound 2 in 15 mL EtOH was added 0.15 mL NEt₃ and 80 mg (0.58 mmol) 2-chloropyridine-5-carbonitrile and the reaction was heated at 80°C for 72 h. After cooling, the reaction was poured

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203
215

into 50 mL H₂O and extracted with CH₂Cl₂. The combined organic layers were dried over MgSO₄, filtered, and the solvent removed by rotary evaporation to yield the crude product. Silica gel chromatography (1% MeOH in EtOAc) yielded 160 mg (73%) of (S)-N-[[3-[3-fluoro-4-{N-(5-cyano-2-pyridyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide as a yellow solid; mp 78-84°C, MS (CI) [M+H]⁺ 454.

Example 15

(S)-N-[[3-[3-Fluoro-4-{N-(α-phenylmethoxycarbonylaminoacetyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide



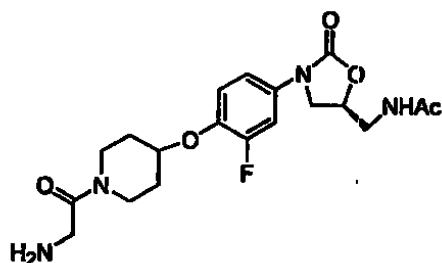
Compound 15

To a solution of 266 mg (0.76 mmol) of Compound 2 in 15 mL CH₂Cl₂ was added 0.2 mL NEt₃ and 188 mg (0.89 mmol) phenylmethoxycarbonylglycine acid fluoride and the reaction was stirred at rt for 1.5 h. Then the reaction was poured into 50 mL sat. NaHCO₃ and extracted with CH₂Cl₂. The combined organic layers were dried over MgSO₄, filtered, and the solvent removed by rotary evaporation afford 375 mg (91%) of crude (S)-N-[[3-[3-fluoro-4-{N-(α-phenylmethoxycarbonylamino acetyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide. ¹H NMR (CDCl₃) δ 7.50 (m, 1H); 7.39 (m, 5H); 7.11 (m, 1H); 7.03 (m, 1H); 6.24 (m, 1H); 5.87 (m, 1H); 5.15 (s, 2H); 4.75 (m, 1H); 4.52 (m, 1H); 4.06 (m, 3H); 3.6-3.8 (m, 6H); 3.37 (m, 1H); 2.10 (s, 3H); and 1.90 (m, 4H).

Example 16

(S)-N-[[3-[3-Fluoro-4-{N-α-aminoacetyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

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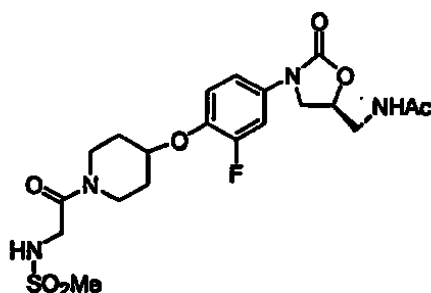


Compound 16

A solution of 340 mg (0.62 mmol) of Compound 15 in 30 mL of EtOH was
5 treated with 36 mg 10% Pd/C, followed by hydrogenation at 50 psi overnight. The suspension was filtered through celite and the filtrate evaporated under reduced pressure to afford crude amine. Trituration of the crude solid with CHCl₃ yielded (S)-N-[[3-[3-fluoro-4-(N-α-amino acetyl)piperidinyl-4-oxy]phenyl]-2-oxo-5-oxazolidinyl]methyl] acetamide; mp 142-146°C, MS (CI) [M+H]⁺ 409.

Example 17

(S)-N-[[3-[3-Fluoro-4-(N-(α-methylsulfonylaminoacetyl)piperidinyl-4-oxy]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide



Compound 17

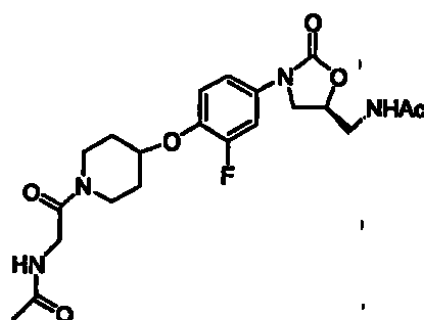
To a solution of 750 mg (4.28 mmol) Boc-glycine in 25 mL CH₂Cl₂ was
added 0.6 mL DAST and the reaction stirred at rt for 20 min. Then the reaction
20 was washed with cold H₂O, the organic layer dried over MgSO₄, filtered, and the solvent removed under reduced pressure to give a brown solid. To a solution of this acid fluoride in 40 mL CH₂Cl₂ was added 327 mg (0.70 mmol) of the TFA salt from Example 2 and 0.23 mL NEt₃ and the reaction stirred at rt for 16 h. The reaction was poured into 50 mL sat. NaHCO₃, extracted with CH₂Cl₂, washed with

245-4A

H₂O, dried over MgSO₄, filtered, and the solvent removed under reduced pressure to give 388 mg of the amide as a beige foam. To a solution of 0.70 mmol of this amide was added 0.55 mL trifluoroacetic acid and the reaction stirred at rt for 20 h. The volatiles were evaporated under reduced pressure to give a brown oil. To this TFA salt in 30 mL CH₂Cl₂ was added 0.23 mL NEt₃ and 0.07 mL (0.90 mmol) methanesulfonyl chloride and the reaction stirred at rt for 18 h. The reaction was poured into 50 mL sat. NaHCO₃, extracted with CH₂Cl₂, washed with H₂O, dried over MgSO₄, filtered, and the solvent removed under reduced pressure to give the crude sulfonamide. Purification by silica gel chromatography (5% MeOH in CH₂Cl₂) yielded 109 mg (32%) of (S)-N-[[3-[3-fluoro-4-{N-(α-methylsulfonylaminoacetyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide as a white foam; mp 78-82°C, MS (CI) [M+H]⁺ 487.

Example 18

(S)-N-[[3-[3-Fluoro-4-{N-(α-N-acetylaminoacetyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide



Compound 18

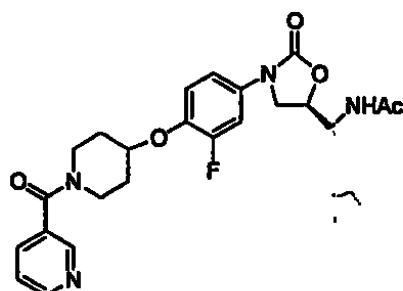
To a solution of 74 mg (0.63 mmol) N-acetylglutamine in 10 mL CH₂Cl₂ was added 125 mg (0.65 mmol) EDCI and the reaction stirred at rt for 2 h. Then a solution of 304 mg (0.65 mmol) TFA salt from Example 2 and 0.15 mL (1.07 mmol) NEt₃ in 10 mL CH₂Cl₂ was added and the reaction stirred at rt for 3 h. The reaction was poured into 10 mL H₂O and extracted with CH₂Cl₂. The combined organic layers were dried over MgSO₄, filtered, and the solvent removed by rotary evaporation to yield the crude product as a yellow oil. Silica gel chromatography (5% MeOH in CH₂Cl₂) yielded 161 mg of (S)-N-[[3-[3-fluoro-4-{N-(α-N-

246 249

acetylaminoacetyl)piperidiny-4-oxy}phenyl]-2-oxo-5-oxazolidinyl)methyl]acetamide; mp 66-68°C, MS (CI) [M+H]⁺ 451.

Example 19

5 (S)-N-[[3-[3-Fluoro-4-{N-(3-pyridoyl)piperidiny-4-oxy}phenyl]-2-oxo-5-oxazolidinyl)methyl]acetamide

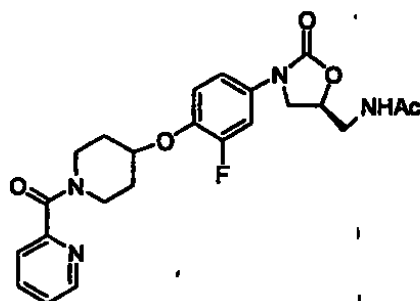


Compound 19

To a solution of 257 mg (0.55 mmol) of the TFA salt in Example 2 in 20 mL CH₂Cl₂ was added 0.4 mL (2.86 mmol) NEt₃ and 105 mg (0.59 mmol) nicotinoyl chloride hydrochloride and the reaction stirred at rt for 20 h. The reaction was poured into 50 mL sat. NaHCO₃ and extracted with CH₂Cl₂. The combined organic layers were washed with H₂O, dried over MgSO₄, filtered, and the solvent removed by rotary evaporation to yield 161 mg (64%) of (S)-N-[[3-[3-fluoro-4-{N-(3-pyridoyl)piperidiny-4-oxy}phenyl]-2-oxo-5-oxazolidinyl)methyl]acetamide; mp 49-53°C, MS (CI) [M+H]⁺ 457.

Example 20

20 (S)-N-[[3-[3-Fluoro-4-{N-(2-pyridoyl)piperidiny-4-oxy}phenyl]-2-oxo-5-oxazolidinyl)methyl]acetamide



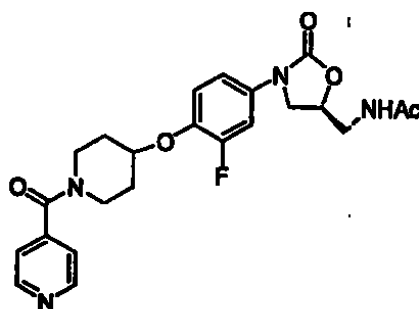
Compound 20

247 249

To a solution of 281 mg (0.60 mmol) of the TFA salt in Example 2 in 50 mL CH_2Cl_2 was added 0.3 mL NEt_3 and 110 mg (0.62 mmol) pyridine 2-carbonyl chloride hydrochloride and the reaction stirred at rt for 72 h. The reaction was poured into 50 mL sat. NaHCO_3 , and extracted with CH_2Cl_2 . The combined organic layers were washed with H_2O , dried over MgSO_4 , filtered, and the solvent removed by rotary evaporation to yield 190 mg (69%) of (S)-N-[[3-[3-fluoro-4-(N-(2-pyridoyl)piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide; mp 55-58°C, MS (CI) $[\text{M}+\text{H}]^+$ 457.

Example 21

(S)-N-[[3-[3-Fluoro-4-(N-(4-pyridoyl)piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide



Compound 21

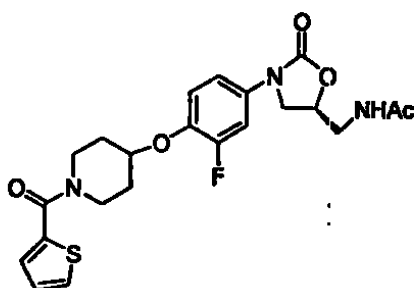
To a solution of 285 mg (0.61 mmol) of the TFA salt in Example 2 in 25 mL CH_2Cl_2 was added 0.5 mL NEt_3 and 123 mg (0.69 mmol) isonicotinoyl chloride hydrochloride and the reaction stirred at rt for 20 h. The reaction was poured into 50 mL sat. NaHCO_3 , and extracted with CH_2Cl_2 . The combined organic layers were washed with H_2O , dried over MgSO_4 , filtered, and the solvent removed by rotary evaporation to yield 29 mg (10%) of (S)-N-[[3-[3-fluoro-4-(N-(4-pyridoyl)piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide as a white foam. ^1H NMR (CDCl_3) δ 8.73 (m, 2H); 7.50 (m, 1H); 7.41 (m, 2H); 7.06 (m, 2H); 6.08 (br t, 1H); 4.69 (m, 1H); 4.54 (m, 1H); 4.04 (m, 1H); 3.90 (m, 2H); 3.6-3.8 (m, 4H); 3.34 (m, 1H); 2.03 (s, 3H); 1.97 (m, 2H); and 1.82 (m, 2H).

Example 22

(S)-N-[[3-[3-Fluoro-4-(N-(2-thienylcarbonyl)piperidinyl-4-oxy)phenyl]-

248
230

2-oxo-5-oxazolidinyl[methyl]acetamide

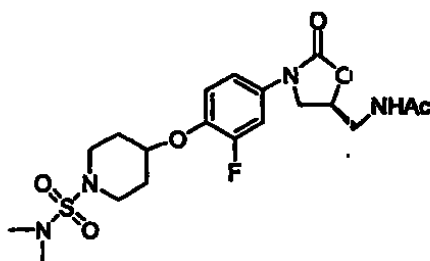


Compound 22

To a solution of 251 mg (0.55 mmol) of the TFA salt in Example 2 in 25 mL CH_2Cl_2 was added 0.2 mL NEt_3 and 0.07 mL (0.65 mmol) 2-thiophenecarbonyl chloride and the reaction stirred at rt for 72 h. The reaction was poured into 50 mL sat. NaHCO_3 and extracted with CH_2Cl_2 . The combined organic layers were washed with H_2O , dried over MgSO_4 , filtered, and the solvent removed by rotary evaporation to give the crude product. The crude material was dissolved in 50 mL CH_2Cl_2 , P-trisamine resin added and the mixture stirred for 2 h. The reaction was filtered and the solvent evaporated under reduced pressure to give (S)-N-[[3-[3-fluoro-4-(N-(2-thienylcarbonyl)piperidin-4-yl)oxy]phenyl]-2-oxo-5-oxazolidinyl]methyl] acetamide; mp 48-51°C, MS (CI) $[\text{M}+\text{H}]^+$ 462.

Example 23

(S)-N-[[3-[3-Fluoro-4-(N-(dimethylsulfamoyl)piperidin-4-yl)oxy]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide



Compound 23

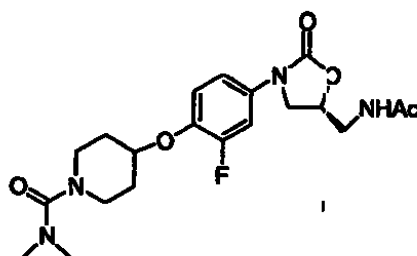
To a solution of 179 mg (0.38 mmol) of the TFA salt in Example 2 in 20 mL CH_2Cl_2 was added 0.12 mL NEt_3 and 0.05 mL (0.47 mmol) dimethylsulfamoyl chloride and the reaction stirred at rt for 18 h. The reaction was poured into 50

247.121

mL sat. NaHCO_3 and extracted with CH_2Cl_2 . The combined organic layers were washed with H_2O , dried over MgSO_4 , filtered, and the solvent removed by rotary evaporation to give the crude product. The crude oil was crystallized from warm $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$ to give (S)-N-[[3-[3-fluoro-4-(N-(dimethylsulfamoyl)piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide as a white solid; mp 132-134°C, MS (CI) $[\text{M}+\text{H}]^+$ 459.

Example 24

(S)-N-[[3-[3-Fluoro-4-(N-(dimethylcarbamoyl)piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

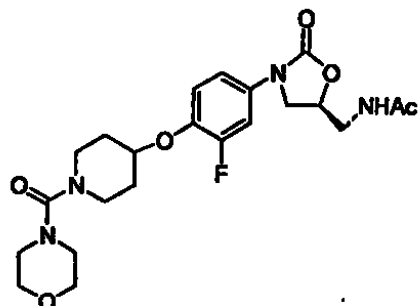


Compound 24

To a solution of 229 mg (0.49 mmol) of the TFA salt in Example 2 in 20 mL CH_2Cl_2 was added 0.15 mL (1.08 mmol) NEt_3 and 0.06 mL (0.65 mmol) dimethylcarbamoylchloride and the reaction stirred at rt overnight. The reaction was poured into 50 mL sat. NaHCO_3 , and extracted with CH_2Cl_2 . The combined organic layers were washed with H_2O , dried over MgSO_4 , filtered, and the solvent removed by rotary evaporation to give the crude product. The crude oil was crystallized from warm $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$ to give 175 mg (85%) of (S)-N-[[3-[3-fluoro-4-(N-(dimethylcarbamoyl)piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide as a white solid; mp 129-131°C, MS (CI) $[\text{M}+\text{H}]^+$ 423.

Example 25

(S)-N-[[3-[3-Fluoro-4-(N-(4-morpholinocarbamoyl)piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

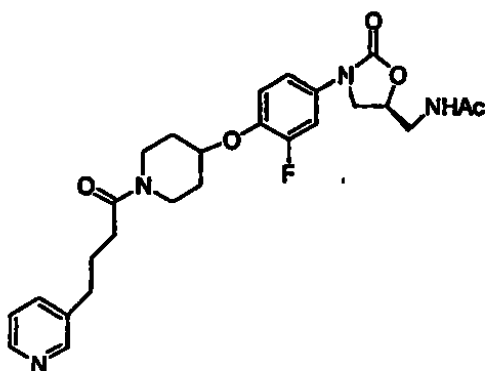


Compound 25

To a solution of 205 mg (0.44 mmol) of the TFA salt in Example 2 in 25 mL CH_2Cl_2 was added 0.13 mL NEt_3 and 0.06 mL (0.51 mmol) 4-morpholinocarbonyl chloride and the reaction stirred for 4 h. The reaction was poured into 50 mL sat. NaHCO_3 and extracted with CH_2Cl_2 . The combined organic layers were washed with H_2O , dried over MgSO_4 , filtered, and the solvent removed by rotary evaporation to give the crude product. The crude product was triturated with Et_2O and hexanes to give 198 mg (97%) of (S)-N-[[3-[3-fluoro-4-{N-(4-morpholinocarbonyl)piperidin-4-yl}oxy]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide as a white solid; mp 167-170°C, MS (CI) $[\text{M}+\text{H}]^+$ 465.

Example 26

(S)-N-[[3-[3-Fluoro-4-{N-(4-pyridin-3-yl-butyl)piperidin-4-yl}oxy]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide



Compound 26

4-Pyridin-3-yl-butynitrile:

251 

To a solution of 0.66 mL (5.11 mmol) 3-pyridine propanol in 5 mL CH₂Cl₂ at 0°C was added 0.62 mL (7.67 mmol) pyridine and 0.47 mL (6.14 mmol) methanesulfonyl chloride and the reaction stirred for 4 h. The solution was concentrated under reduced pressure and the crude mesylate dissolved in 10 mL DMF. To this solution was added 902 mg (18.41 mmol) sodium cyanide and the reaction stirred at 60°C for 3 days. Then the solution was cooled, diluted with H₂O (30 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with H₂O, dried over MgSO₄, and the solvent removed under reduced pressure to give a dark red oil. The crude nitrile was purified by dissolving in EtOAc, washing with H₂O, concentrating, and filtering through a silica gel plug (5% MeOH in CH₂Cl₂) to yield 425 mg (57%) of the nitrile.

4-Pyridin-3-yl-butyric acid:

A solution of 425 mg (2.91 mmol) of 4-pyridin-3-yl-butyronitrile in 15 mL conc. HCl was refluxed for 8 h. The volatiles were evaporated under reduced pressure and the residue dissolved in EtOH. Upon addition of acetone and cooling a dark brown solid precipitated. The filtrate was concentrated and triturated with cold acetone to collect a total of 334 mg (69%) of the carboxylic acid.

4-Pyridin-3-yl-butyryl chloride:

To a solution of 247 mg (1.49 mmol) of 4-pyridin-3-yl-butyric acid in 10 mL CH₂Cl₂ was added one drop DMF and 2.3 mL (4.56 mmol) oxalyl chloride and the mixture stirred at rt for 4 h. The volatiles were evaporated under reduced pressure and the material used crude in the following procedure.

(S)-N-[13-[3-fluoro-4-(N-(4-pyridin-3-yl-butyryl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (Compound 26):

To a solution of 597 mg (1.29 mmol) of the TFA salt in Example 2 in 20 mL CH₂Cl₂ was added 0.54 mL (3.86 mmol) NEt₃ at 0°C and the reaction stirred for 30 min, warming to rt. Then the solution was cooled to 0°C, a solution of the previous acid chloride in 20 mL CH₂Cl₂ was added, and the reaction allowed to warm to rt. The reaction was diluted with CH₂Cl₂, washed with sat. NaHCO₃ (2 x

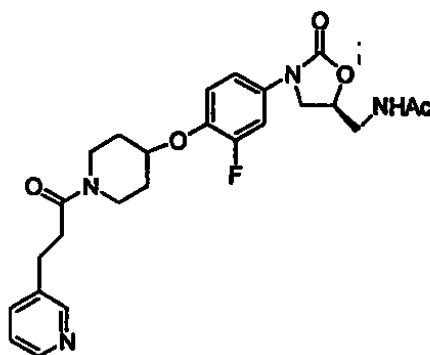
252 *252*

30 mL), washed with H₂O (2 x 30 mL), dried over MgSO₄, filtered, and the solvent removed by rotary evaporation to give the crude product as a tan foam.

Purification by silica gel chromatography (10% MeOH in EtOAc) yielded 152 mg (24%) of (S)-N-[[3-[3-fluoro-4-(N-(4-pyridin-3-yl-butyl)piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide as an off-white foam; mp 42-45°C, MS (CI) [M+H]⁺ 499.

Example 27

(S)-N-[[3-[3-Fluoro-4-(N-(3-pyridin-3-yl-propionyl)piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide



Compound 27

3-Pyridine propionyl chloride:

To a solution of 300 mg (1.99 mmol) 3-pyridine propionic acid in 10 mL CH₂Cl₂ was added one drop DMF and 2.3 mL (4.56 mmol) oxalyl chloride, and the mixture stirred at rt for 4 h. The volatiles were evaporated under reduced pressure and the material used crude in the following procedure.

(S)-N-[[3-[3-fluoro-4-(N-(3-pyridin-3-yl-propionyl)piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (Compound 27):

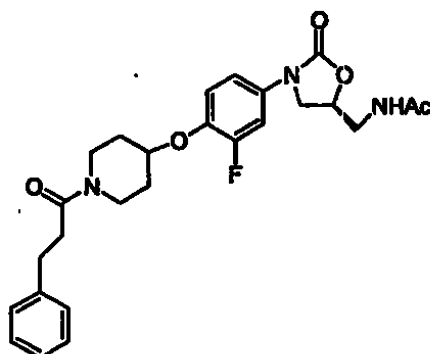
To a solution of 917 mg (1.97 mmol) of the TFA salt in Example 2 in 20 mL CH₂Cl₂ was added 0.75 mL (5.41 mmol) NEt₃ at 0°C and the reaction stirred for 30 min, warming to rt. Then the solution was cooled to 0°C, a solution of the previous acid chloride in 20 mL CH₂Cl₂ was added along with an additional equivalent of NEt₃, and the reaction allowed to warm to rt and stirred overnight. The reaction was diluted with CH₂Cl₂, washed with sat. NaHCO₃ (2 x 30 mL),

253.5

washed with H₂O (2 x 30 mL), dried over Na₂SO₄, filtered, and the solvent removed by rotary evaporation to give the crude product as a dark orange oil. Purification by silica gel chromatography (10% MeOH and 1% NEt₃ in EtOAc) yielded 110 mg of (S)-N-[[3-[3-fluoro-4-(N-(3-pyridin-3-yl-propionyl)piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide as a foam; mp 45-47°C, MS (CI) [M+H]⁺ 485.

Example 28

(S)-N-[[3-[3-Fluoro-4-(N-(3-phenyl-propionyl)piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide



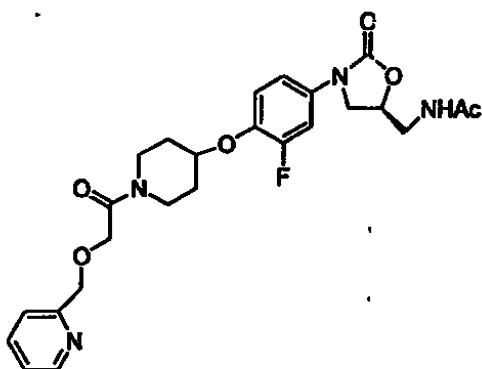
Compound 28

To a solution of 133 mg (0.27 mmol) of the TFA salt in Example 2 in 20 mL CH₂Cl₂ was added 0.07 mL (0.53 mmol) NEt₃ and 0.04 mL (0.29 mmol) hydrocinnamoyl chloride, and the reaction allowed to warm to rt and stirred for 1 h. The reaction was diluted with CH₂Cl₂, washed with sat. NaHCO₃ (2 x 30 mL), washed with H₂O (2 x 30 mL), dried over Na₂SO₄, filtered, and the solvent removed by rotary evaporation to give the crude product as a colorless oil. Purification by silica gel chromatography (10% MeOH in EtOAc) yielded a transparent glass. This material was triturated with EtOAc and hexanes to give (S)-N-[[3-[3-fluoro-4-(N-(3-phenyl-propionyl)piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide as a white solid; MS (CI) [M+H]⁺ 484.

Example 29

(S)-N-[[3-[4-(N-(Pyridin-2-ylmethoxyacetyl)piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

254
256



Compound 29

(Pyridin-2-yl-methoxy)-acetic acid *t*-butyl ester:

To a solution of 0.5 mL (5.18 mmol) 2-pyridylmethanol in 20 mL THF at 0°C was added 270 mg (6.75 mmol) NaH and the reaction stirred for 0.25 h. Then 0.82 mL *t*-butylbromoacetate was added and the reaction warmed to rt and stirred for 12 days. The reaction was poured into 100 mL H₂O, extracted with CH₂Cl₂ (2 x 100 mL), the combined organic layers washed with brine, dried over MgSO₄, filtered, and the solvent removed under reduced pressure to give 1.16 g (61%) as a brown oil.

(Pyridin-2-yl-methoxy)-acetic acid:

To a solution of 706 mg (3.16 mmol) of (pyridin-3-yl-methoxy)-acetic acid *t*-butyl ester and 1.5 mL of TFA in 25 mL of methylene chloride were stirred at room temperature for 20 hr. The volatiles were evaporated to afford crude acid.

(S)-N-[[3-[4-[N-(Pyridin-2-ylmethoxyacetyl)piperidin-4-yl]oxy]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (Compound 29):

To 460 mg (1.63 mmol) of (pyridin-2-yl-methoxy)acetic acid in 100 mL CH₂Cl₂ was added 405 mg (2.11 mmol) EDCI, 634 mg (1.36 mmol) of the TFA salt from example 1, and 4.5 mL (32.2 mmol) NEt₃. The reaction was stirred at rt for 5 days. Then the mixture was poured into 125 mL H₂O, extracted with CH₂Cl₂, the organic layers washed with brine, dried over MgSO₄, filtered, and the solvent removed by rotary evaporation. Purification by silica gel chromatography (5% MeOH in CH₂Cl₂) yielded 403 mg (59%) of (S)-N-[[3-[4-[N-(pyridin-2-ylmethoxyacetyl)piperidin-4-yl]oxy]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

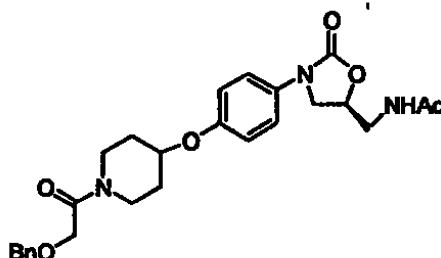
255

as a yellow semi-solid. ^1H NMR (CDCl_3) δ 8.54 (m, 1H); 7.72 (m, 1H); 7.49 (m, 2H); 7.23 (m, 1H); 7.09 (m, 1H); 7.00 (m, 1H); 6.10 (m, 1H); 4.78 (m, 1H); 4.71 (s, 2H); 4.48 (m, 1H); 4.32 (s, 2H); 4.04 (m, 1H); 3.6-3.8 (m, 6H); 3.45 (m, 1H); 2.03 (s, 3H); and 1.83 (m, 4H).

5

Example 30

(S)-N-[[3-[4-{N-(Benzyloxyacetyl)piperidiny-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide



Compound 30

1-[N-(*t*-Butoxycarbonyl)piperidiny-4-oxy]-4-nitrobenzene:

To a solution of 10.0 g (49.68 mmol) of N-(*t*-butoxycarbonyl)-4-piperidinol from example 1 in 125 mL dry THF at 0°C was added dropwise 74 mL (74.53 mmol) 1M KO^tBu. After stirring at 0°C for 0.5 h, 5.27 mL (49.68 mmol) *p*-fluoronitrobenzene was added and the reaction warmed to rt and stirred overnight. The volatiles were removed under reduced pressure and the reaction diluted with 800 mL H₂O. The mixture was extracted with CH₂Cl₂ (2 x 500 mL) and a brown solid removed by filtration. The combined aqueous layers were washed with H₂O, dried with MgSO₄, filtered, and the solvent removed by rotary evaporation to give an orange solid. Purification by silica gel chromatography (3:1 hexane:EtOAc) yielded 6.98 g (44%) of 1-[N-(*t*-butoxycarbonyl)piperidiny-4-oxy]-4-nitrobenzene as a pale yellow solid. An additional 3.20 g of product was extracted from the brown solid; MS (CI) [M+Na]⁺ 345.

1-[4-(N-*t*-Butoxycarbonyl)piperidiny-4-oxy]-4-aminobenzene:

To 6.97 g (21.62 mmol) of 1-[N-(*t*-butoxycarbonyl)piperidiny-4-oxy]-4-nitrobenzene in 250 mL MeOH was added 6.81 g (108.1 mmol) ammonium-formate and a catalytic amount of 10% Pd/C, and the reaction heated at 50°C

256
105

under N₂ for 5 h. The reaction was filtered through a pad of celite and the filtrate evaporated to afford crude aniline as an orange oil. The material was used without further purification in the next step.

5 1-[N-(*t*-Butoxycarbonyl)piperidinyl-4-oxy]-4-(phenylmethoxycarbonylamino)benzene:

To 6.32 g (21.62 mmol) of 1-[4-(*N*-*t*-butoxycarbonyl)piperidinyl-4-oxy]-4-aminobenzene in 300 mL 2:1 acetone:H₂O at 0°C was added 4.50 g (52.97 mmol) NaHCO₃ and 3.30 mL (23.13 mmol) benzylchloroformate. The reaction was
10 allowed to warm to rt and stirred overnight. Then the volatiles were evaporated, the residue diluted with 200 mL H₂O and extracted with Et₂O (2 x 200 mL). The combined organic layers were washed with H₂O, dried over MgSO₄, filtered, and the solvent removed by rotary evaporation to give 8.62 g (93%) of 4-[N-(*t*-butoxycarbonyl)piperidinyl-4-oxy]-1-(phenylmethoxycarbonylamino)benzene as a pink solid; mp 107-108°C, MS (CI) [M+Na]⁺ 449.

(R)-[3-[4-[N-(*t*-Butoxycarbonyl)piperidinyl-4-oxy]phenyl]-2-oxo-5-oxazolidinyl]methanol:

To 8.23 g (19.31 mmol) of 4-[N-(*t*-butoxycarbonyl)piperidinyl-4-oxy]-1-(phenylmethoxycarbonylamino)benzene in 300 mL dry THF at -78°C was added 10.8 mL (27.03 mmol) 2.5M *n*-BuLi and the reaction stirred for 1 h. Then 3.84 mL (27.03 mmol) (R)-glycidyl butyrate was added via syringe and the reaction warmed to rt and stirred for 3 days. Then an additional 2 mL 2.5M *n*-BuLi was added and the reaction stirred for another day. The reaction was carefully poured
25 into 150 mL sat. NH₄Cl (aq.) and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with H₂O, dried over MgSO₄, filtered, and the solvent removed by rotary evaporation. Silica gel chromatography (EtOAc) gave 4.34 g (57%) of (R)-[3-[4-[N-(*t*-butoxycarbonyl)piperidinyl-4-oxy]phenyl]-2-oxo-5-oxazolidinyl]methanol as a yellow solid; mp 110-112°C, MS (CI) [M+Na]⁺
30 415.

(R)-[3-[4-[N-(*t*-Butoxycarbonyl)piperidinyl-4-oxy]phenyl]-2-oxo-5-oxazolidinyl]methyl methanesulfonate:

257.9

To 4.23 g (10.79 mmol) of (R)-[3-[4-[N-(t-butoxycarbonyl)piperidinyl-4-oxy]phenyl]-2-oxo-5-oxazolidinyl]methanol in 75 mL CH₂Cl₂ at 0°C was added 3.0 mL (21.58 mmol) NEt₃ and 1.2 mL (15.11 mmol) methanesulfonyl chloride. The reaction was allowed to warm to rt over an hour and washed with H₂O (2 x 50 mL), dried over MgSO₄, filtered, and the solvent removed by rotary evaporation to yield 5.0 g (99%) of (S)-[3-[4-[N-(t-butoxycarbonyl)piperidinyl-4-oxy]phenyl]-2-oxo-5-oxazolidinyl]methyl methanesulfonate as a white foam.

(R)-[3-[4-[N-(t-Butoxycarbonyl)piperidinyl-4-oxy]phenyl]-2-oxo-5-oxazolidinyl]methylazide:

To a solution of 5.0 g (10.63 mmol) of (R)-[3-[4-[N-(t-butoxycarbonyl)piperidinyl-4-oxy]phenyl]-2-oxo-5-oxazolidinyl]methyl methanesulfonate in 100 mL DMF was added 2.63 g (40.38 mmol) sodium azide and the reaction was heated at 70°C overnight. Then the reaction was poured into 200 mL H₂O and extracted with EtOAc (3 x 150 mL). The combined organic layers were washed with H₂O (2 x 150 mL), dried over MgSO₄, filtered, and the solvent removed by rotary evaporation to yield 4.4 g (99%) of (R)-[3-[4-[N-(t-butoxycarbonyl)piperidinyl-4-oxy]phenyl]-2-oxo-5-oxazolidinyl]methylazide as a yellow oil; MS (CI) [M+Na]⁺ 440.

(S)-N-[[3-[4-[N-(t-Butoxycarbonyl)piperidinyl-4-oxy]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide:

A solution of 4.48 g (10.73 mmol) of (R)-[3-[4-[N-(t-Butoxycarbonyl)piperidinyl-4-oxy]phenyl]-2-oxo-5-oxazolidinyl]methylazide in 30 mL of EtOAc was treated with a catalytic amount of 10% Pd/C, followed by hydrogenation at 50 psi for 20 h. To this mixture at 0°C was added 1.1 mL (12.88 mmol) pyridine and 3.2 mL (34.34 mmol) acetic anhydride. The reaction was stirred for 30 min at 0°C, then warmed to rt over 1 h. The reaction was filtered through celite, eluting with EtOAc. The volatiles were removed under reduced pressure and the yellow solid dissolved in EtOAc and washed with H₂O (3 x 100 mL). A white solid was removed via filtration. The organic layers were concentrated to an orange oil and triturated using EtOAc and hexanes to yield a white solid. The white solids were combined to yield 1.48 g (31%) of (S)-N-[[3-[4-[N-(t-butoxycarbonyl)piperidinyl-4-

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oxy)phenyl]-2-oxo-5-oxazolidinyl)methyl]acetamide; mp 185-186°C, MS (CI) [M+Na]⁺ 456.

(S)-N-[[3-[4-(Piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl)methyl]acetamide:

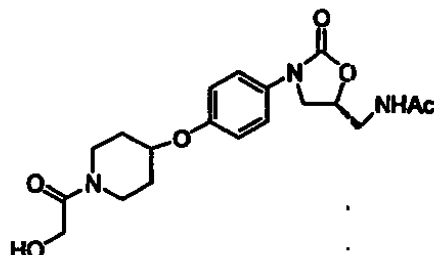
5 To a solution of 1.48 g (3.41 mmol) of the previous Boc-carbamate ((S)-N-[[3-[4-(N-(t-butoxycarbonyl)piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl)methyl]acetamide) in 225 mL CH₂Cl₂ was added 2.6 mL (34.14 mmol) trifluoroacetic acid and the reaction stirred at rt for 2 h. The reaction was diluted with 50 mL CH₂Cl₂, washed with NaHCO₃ (2 x 100 mL), dried over MgSO₄,
10 filtered, and evaporated under reduced pressure to yield 980 mg (86%) of (S)-N-[[3-[4-(piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl)methyl]acetamide as a yellow oil.

(S)-N-[[3-[4-(N-(Benzyloxyacetyl)piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl)methyl]acetamide:

To a suspension of 160 mg (0.48 mmol) of (S)-N-[[3-[4-(piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl)methyl]acetamide in 20 mL CH₂Cl₂ was added 0.13 mL (0.96 mmol) NEt₃ and 0.08 mL (0.53 mmol) benzyloxyacetyl chloride. After stirring for 2 h, the reaction was poured into 75 mL H₂O and extracted with CH₂Cl₂ (4 x 50 mL). The combined organic layers were dried over MgSO₄, filtered, and evaporated under reduced pressure. Silica gel chromatography (10% MeOH in EtOAc) afforded (S)-N-[[3-[4-(N-(benzyloxyacetyl)piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl)methyl] acetamide as a white foam; mp 53-55°C, MS (CI) [M+H]⁺ 482.

Example 31

(S)-N-[[3-[4-(N-(α-Hydroxyacetyl)piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl)methyl]acetamide



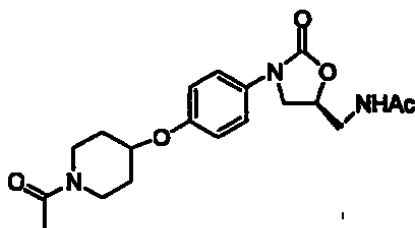
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Compound 31

To a solution of 103 mg (0.21 mmol) of Compound 30 in 10 mL MeOH was added 67 mg (1.07 mmol) ammonium formate and a catalytic amount of 10% Pd/C, and the reaction was heated at 50°C for 3 days. Then the reaction was filtered through a pad of celite, eluted with EtOAc and MeOH, and the solvent removed under reduced pressure to yield 56 mg (66%) of (S)-N-[[3-[4-(N-(α-hydroxyacetyl)piperidiny-4-oxy)phenyl]-2-oxo-5-oxazolidiny-1-yl]methyl]acetamide as a white foam; MS (CI) [M+H]⁺ 392.

Example 32

(S)-N-[[3-[4-(N-(Acetyl)piperidiny-4-oxy)phenyl]-2-oxo-5-oxazolidiny-1-yl]methyl]acetamide



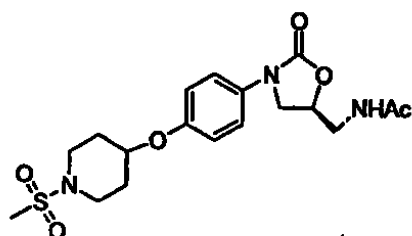
Compound 32

To a solution of 240 mg (0.72 mmol) of (S)-N-[[3-[4-(piperidiny-4-oxy)phenyl]-2-oxo-5-oxazolidiny-1-yl]methyl]acetamide in 20 mL CH₂Cl₂ was added 0.45 mL (3.24 mmol) NEt₃ and 0.08 mL (1.08 mmol) acetyl chloride and the reaction stirred overnight. The reaction was diluted with 50 mL CH₂Cl₂, washed with H₂O, dried over MgSO₄, filtered, and the solvent removed by rotary evaporation to give the crude product as a gold oil. Purification by silica gel chromatography (10% MeOH in EtOAc) yielded 130 mg (50%) of (S)-N-[[3-[4-(N-(acetyl)piperidiny-4-oxy)phenyl]-2-oxo-5-oxazolidiny-1-yl]methyl]acetamide as a colorless oil; MS (CI) [M+Na]⁺ 398.

Example 33

(S)-N-[[3-[4-(N-(Methanesulfonyl)piperidiny-4-oxy)phenyl]-2-oxo-5-oxazolidiny-1-yl]methyl]acetamide

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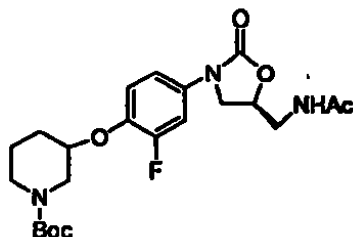


Compound 33

To a solution of 50 mg (0.15 mmol) of (S)-N-[[3-[4-(piperidin-4-oxo-5-oxazolidinyl)methyl]acetamide in 20 mL CH₂Cl₂ was added 0.04 mL (0.30 mmol) NEt₃ and 0.02 mL (0.21 mmol) methanesulfonyl chloride and the reaction stirred overnight. The reaction was diluted with 10 mL CH₂Cl₂, washed with H₂O, dried over MgSO₄, filtered, and the solvent removed by rotary evaporation to give the crude product as a gold oil. Purification by silica gel chromatography (10% MeOH in EtOAc) yielded 40 mg (64%) of (S)-N-[[3-[4-(N-(methanesulfonyl)piperidin-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide as a white solid; MS (CI) [M+Na]⁺ 434.

Example 34

(S)-N-[[3-[3-Fluoro-4-(N-(*t*-butoxycarbonyl)piperidin-3-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide



Compound 34

20 N-(*t*-Butoxycarbonyl)-3-piperidinol:

A solution of 10.0 g (72.67 mmol) 3-hydroxypiperidine in 100 mL dry THF at 0°C was added 10.1 mL (72.67 mmol) NEt₃ and 15.86 g (72.67 mmol) di-*t*-butylcarbonate in 100 mL THF and the reaction allowed to warm to rt and stirred overnight. The solvent was removed under reduced pressure, the resulting
25 residue dissolved in 300 mL CH₂Cl₂ and the solution extracted with H₂O (2 x 200

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mL), dried over MgSO_4 , filtered and rotary evaporated to yield 12.66 g (87%) of N-(*t*-butoxycarbonyl)-3-piperidinol as an oil which slowly solidified to a white solid.

1-[N-(*t*-Butoxycarbonyl)piperidinyl-3-oxy]-2-fluoro-4-nitrobenzene:

5 To a solution of 5.0 g (24.84 mmol) of N-(*t*-butoxycarbonyl)-3-piperidinol in 75 mL dry THF at 0°C was added dropwise 37 mL (37.26 mmol) 1M KO^tBu. After stirring at 0°C for 0.5 h, 2.8 mL (24.84 mmol) 3,4-difluoronitrobenzene was added and the reaction warmed to rt and stirred for 0.5 h. The volatiles were removed under reduced pressure and the residue was dissolved in 400 mL H_2O and
10 extracted with CH_2Cl_2 (2 x 300 mL). The combined aqueous layers were dried with MgSO_4 , filtered, and the solvent removed by rotary evaporation. Purification by silica gel chromatography (3:1 hexanes:EtOAc) yielded 5.94 g (70%) of 1-[N-(*t*-butoxycarbonyl)piperidinyl-3-oxy]-2-fluoro-4-nitrobenzene; MS (CI) $[\text{M}+\text{Na}]^+$ 363.

1-[4-(N-(*t*-Butoxycarbonyl)piperidinyl-3-oxy)-2-fluoro-4-aminobenzene:

15 To 5.94 g (17.40 mmol) of 1-[N-(*t*-butoxycarbonyl)piperidinyl-3-oxy]-2-fluoro-4-nitrobenzene in 200 mL MeOH was added 5.49 g (87.02 mmol) ammonium formate and a catalytic amount of 10% Pd/C, and the reaction heated at 50°C under N_2 overnight. The reaction was filtered through a pad of celite and
20 the filtrate evaporated to afford crude aniline as an orange oil. The product was dissolved in 150 mL EtOAc and washed with H_2O (2 x 100), dried over MgSO_4 , filtered, and the solvent removed under reduced pressure to give 4.98 g (92%) as a light yellow oil. The material was used without further purification in the next step.

2-Fluoro-1-[N-(*t*-butoxycarbonyl)piperidinyl-3-oxy]-4-(phenylmethoxy carbonylamino)benzene:

25 To 4.98 g (16.08 mmol) of 1-[4-(N-(*t*-butoxycarbonyl)piperidinyl-3-oxy)-2-fluoro-4-aminobenzene in 300 mL 2:1 acetone: H_2O at 0°C was added 3.31 g
30 (39.40 mmol) NaHCO_3 and 2.46 mL (17.20 mmol) benzylchloroformate. After stirring at rt overnight the volatiles were evaporated, the residue diluted with 200 mL H_2O and extracted with Et_2O (3 x 150 mL). The combined organic layers were washed with H_2O , dried over MgSO_4 , filtered, and the solvent removed by rotary

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evaporation. Silica gel chromatography (2:3 EtOAc:Hexanes) afforded 5.30 g (75%) of 3-fluoro-4-{N-(*t*-butoxycarbonyl)piperidinyl-3-oxy}-1-(phenylmethoxycarbonylamino)benzene as a white solid; mp 109-110°C, MS (CI) [M+Na]⁺ 467.

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(R)-[3-[3-Fluoro-4-{N-(*t*-butoxycarbonyl)piperidinyl-3-oxy}phenyl]-2-oxo-5-oxazolidinyl]methanol:

To 3.27 g (7.36 mmol) of 2-fluoro-1-{N-(*t*-butoxycarbonyl)piperidinyl-3-oxy}-4-(phenylmethoxycarbonylamino)benzene in 150 mL dry THF at -78°C was added 4.1 mL (10.31 mmol) 2.5M *n*-BuLi and the reaction stirred for 1 h. Then 1.5 mL (10.31 mmol) (*R*)-glycidyl butyrate was added via syringe and the reaction warmed to rt and stirred overnight. The reaction was carefully poured into 100 mL sat. NH₄Cl (aq.) and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with H₂O, dried over MgSO₄, filtered, and the solvent removed by rotary evaporation. Silica gel chromatography (EtOAc) gave 2.99 g (98%) of (*R*)-[3-[3-fluoro-4-{N-(*t*-butoxycarbonyl)piperidinyl-3-oxy}phenyl]-2-oxo-5-oxazolidinyl]methanol as a white foam; mp 48-50°C.

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(R)-[3-[3-Fluoro-4-{N-(*t*-butoxycarbonyl)piperidinyl-3-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl methanesulfonate:

To 1.32 g (3.22 mmol) of (*R*)-[3-[3-fluoro-4-{N-(*t*-butoxycarbonyl)piperidinyl-3-oxy}phenyl]-2-oxo-5-oxazolidinyl]methanol in 50 mL CH₂Cl₂ at 0°C was added 0.90 mL (6.44 mmol) NEt₃ and 0.35 mL (4.51 mmol) methanesulfonyl chloride. The reaction was allowed to warm to rt over 1 h and then washed with H₂O (2 x 30 mL), dried over MgSO₄, filtered and the solvent removed by rotary evaporation to yield 1.50 g (95%) of (*R*)-[3-[3-fluoro-4-{N-(*t*-butoxycarbonyl)piperidinyl-3-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl methanesulfonate as a yellow foam.

5

(R)-[3-[3-Fluoro-4-{N-(*t*-butoxycarbonyl)piperidinyl-3-oxy}phenyl]-2-oxo-5-oxazolidinyl]methylazide:

To a solution of 1.50 g (3.07 mmol) of (*R*)-[3-[3-fluoro-4-{N-(*t*-butoxycarbonyl)piperidinyl-3-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl

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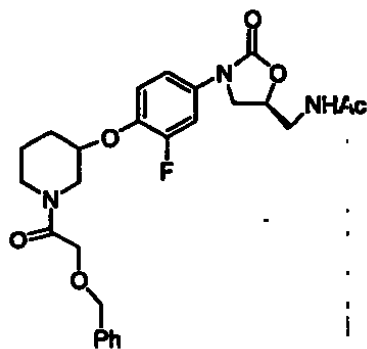
methanesulfonate in 60 mL DMF was added 758 mg (11.66 mmol) sodium azide and the reaction heated at 75°C overnight. Then the reaction was poured into 100 mL H₂O and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with H₂O (3 x 200 mL), dried over MgSO₄, filtered, and the solvent removed by rotary evaporation to yield (R)-[3-[3-fluoro-4-(N-(t-butoxycarbonyl)piperidinyl-3-oxy)phenyl]-2-oxo-5-oxazolidinyl]methylazide as a foam.

(S)-N-[[3-[3-Fluoro-4-{ N-(t-butoxycarbonyl)piperidinyl-3-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide:

A solution of 1.34 g (3.07 mmol) of (R)-[3-[3-fluoro-4-(N-(t-butoxycarbonyl)piperidinyl-3-oxy)phenyl]-2-oxo-5-oxazolidinyl]methylazide in 30 mL of EtOAc was treated with a catalytic amount of 10% Pd/C, followed by hydrogenation at 50 psi for 20 h. To this mixture at 0°C was added 0.3 mL (3.68 mmol) pyridine and 0.93 mL (9.82 mmol) acetic anhydride. The reaction was stirred for 30 min at 0°C, then warmed to rt over 1 h. The reaction was filtered through celite, eluting with EtOAc. The volatiles were removed under reduced pressure. Silica gel chromatography (10% MeOH in EtOAc) yielded (S)-N-[[3-[4-(N-(t-butoxycarbonyl)piperidinyl-3-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide as a white solid; mp 60-63°C, MS (CI) [M+Na]⁺ 474.

Example 35

(S)-N-[[3-[3-Fluoro-4-(N-(benzyloxyacetyl)piperidinyl-3-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide



Compound 35

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(S)-N-[[3-[3-Fluoro-4-(piperidinyl-3-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide:

To a solution of 589 mg (1.31 mmol) of Compound 34 in 13 mL CH₂Cl₂ was added 1.0 mL (13.1 mmol) trifluoroacetic acid and the reaction stirred at rt for 2 h.

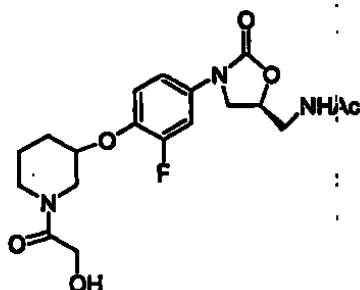
- 5 The volatiles were evaporated under reduced pressure to yield (S)-N-[[3-[3-fluoro-4-(piperidinyl-3-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide:

(S)-N-[[3-[3-Fluoro-4-(N-(benzyloxyacetyl)piperidinyl-3-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide:

- 10 To a suspension of 303 mg (0.65 mmol) of (S)-N-[[3-[3-fluoro-4-(piperidinyl-3-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide in 50 mL CH₂Cl₂ was added 0.27 mL (1.96 mmol) NEt₃ and 0.11 mL (0.72 mmol) benzyloxyacetyl chloride. After stirring for 1 h, the reaction was poured into 75 mL H₂O and extracted with CH₂Cl₂ (4 x 50 mL). The combined organic layers were dried over MgSO₄, filtered, and evaporated under reduced pressure to yield (S)-N-[[3-[3-fluoro-4-(N-(benzyloxyacetyl)piperidinyl-3-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl] acetamide as a foam; MS (CI) [M+H]⁺ 500.

Example 36

(S)-N-[[3-[3-Fluoro-4-(N-(α-hydroxyacetyl)piperidinyl-3-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide



Compound 36

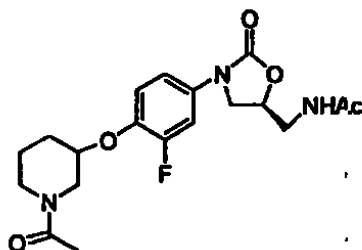
- 25 To a solution of 301 mg (0.60 mmol) of Compound 35 in 10 mL MeOH was added 190 mg ammonium formate and a catalytic amount of 10% Pd/C and the reaction was heated at reflux overnight. Then the reaction was filtered through a pad of celite and the solvent removed under reduced pressure. Silica gel chromatography (10% MeOH in EtOAc) afforded 231 mg (82%) of (S)-N-[[3-[3-

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fluoro-4-{N-(α -hydroxyacetyl)piperidinyl-3-oxy}phenyl]-2-oxo-5-oxazolidinyl)methyl]acetamide as a yellow foam; MS (CI) [M+H]⁺ 410.

Example 37

(S)-N-[[3-[3-Fluoro-4-{N-(acetyl)piperidinyl-3-oxy}phenyl]-2-oxo-5-oxazolidinyl)methyl]acetamide

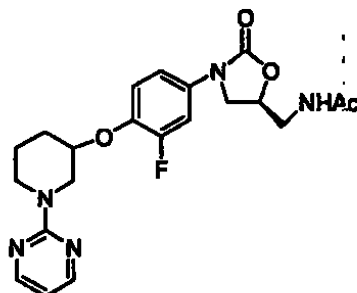


Compound 37

To a solution of 100 mg (0.28 mmol) of (S)-N-[[3-[3-fluoro-4-{piperidinyl-3-oxy}phenyl]-2-oxo-5-oxazolidinyl)methyl]acetamide in 10 mL CH₂Cl₂ was added 0.12 mL (0.85 mmol) NEt₃ and 0.03 mL (0.43 mmol) acetyl chloride. The reaction stirred at rt for 2 h diluted with CH₂Cl₂, washed with H₂O (2 x 100 mL), dried over MgSO₄, filtered, and the solvent removed by rotary evaporation to yield the impure amide. Purification by silica gel chromatography (10% MeOH in EtOAc) and trituration of the resultant oil with EtOAc and hexanes yielded (S)-N-[[3-[3-fluoro-4-{N-(acetyl)piperidinyl-3-oxy}phenyl]-2-oxo-5-oxazolidinyl)methyl]acetamide as a solid.

Example 38

(S)-N-[[3-[3-Fluoro-4-{N-(2-pyrimidinyl)piperidinyl-3-oxy}phenyl]-2-oxo-5-oxazolidinyl)methyl]acetamide



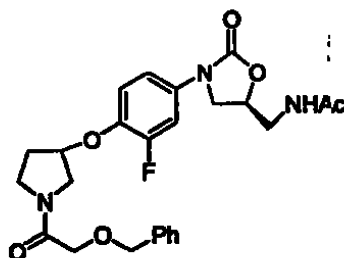
Compound 38

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To a solution of 151 mg (0.33 mmol) of (S)-N-[[3-[3-fluoro-4-(piperidinyl-3-oxo-5-oxazolidinyl)methyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide in 4 mL EtOH was added 0.11 mL (0.82 mmol) NEt₃ and 39 mg (0.34 mmol) 2-chloropyrimidine and the reaction heated at reflux for 3 days. The reaction was cooled, poured into 15 mL NaHCO₃ (sat.), extracted with CH₂Cl₂, washed with H₂O (2 x 100 mL), dried over MgSO₄, filtered, and the solvent removed by rotary evaporation to yield an orange oil. The crude oil was triturated with EtOAc and Et₂O to give 25mg (23%) of (S)-N-[[3-[3-fluoro-4-(N-(2-pyrimidinyl)piperidinyl-3-oxo-5-oxazolidinyl)methyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide as a pale orange solid; mp 130-131°C, MS (CI) [M+H]⁺ 429.

Example 39

(S)-N-[[3-[3-Fluoro-4-(N-(benzyloxyacetyl)pyrrolidinyl-3-oxo-5-oxazolidinyl)methyl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide



Compound 39

N-(Benzyloxyacetyl)-3-pyrrolidinol:

A solution of 4.4 mL (52.93 mmol) 3-pyrrolidinol in 250 mL CH₂Cl₂ at 0°C was added 8.4 mL (60.26 mmol) NEt₃ and 8.2 mL (51.97 mmol) benzyloxyacetyl chloride. The reaction was stirred for 3.5 h and then poured into 400 mL H₂O. The reaction was extracted with CH₂Cl₂, dried over MgSO₄, filtered and rotary evaporated to yield 12.0 g (98%) of N-(benzyloxyacetyl)-3-pyrrolidinol as a yellow oil.

1-[N-(Benzyloxyacetyl)pyrrolidinyl-3-oxyl]-2-fluoro-4-nitrobenzene:

To a solution of 2.03 g (8.63 mmol) of N-(benzyloxyacetamide)-3-pyrrolidinol in 50 mL dry THF at 0°C was added dropwise 10 mL (10.0 mmol) 1M

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KOtBu. After stirring at 0°C for 0.5 h, 0.96 mL (8.67 mmol) 3,4-difluoronitrobenzene was added and the reaction warmed to rt and stirred overnight. The reaction was poured into 100 mL H₂O and extracted with EtOAc. The combined organic layers were washed with H₂O, dried with MgSO₄, filtered, and the solvent removed by rotary evaporation. Then the solid was recrystallized from EtOAc and hexanes to afford 2.49 g (77%) of 1-[N-(benzyloxyacetyl)pyrrolidinyl-3-oxy]-2-fluoro-4-nitrobenzene as a solid.

1-[4-(N-Benzyloxyacetyl)pyrrolidinyl-3-oxy]-2-fluoro-4-aminobenzene:

To 1.61 g (4.31 mmol) of 1-[N-(benzyloxyacetamide)pyrrolidinyl-3-oxy]-2-fluoro-4-nitrobenzene in 50 mL EtOH was added 4.86 g (21.5 mmol) SnCl₂ and the reaction heated at 70°C for 2 h. The reaction was poured into ice water and extracted with EtOAc and CHCl₃ (2 x 100 mL). The combined organic layers were dried over MgSO₄, filtered, and the solvent removed under reduced pressure to give 880 mg (58%) of 1-[4-(N-benzyloxyacetamide)pyrrolidinyl-3-oxy]-2-fluoro-4-aminobenzene as a yellow oil. The material was used without further purification in the next step.

2-Fluoro-1-[N-(benzyloxyacetyl)pyrrolidinyl-3-oxy]-4-(phenylmethoxycarbonylamino)benzene:

To 466 mg (2.73 mmol) of 1-[4-(N-benzyloxyacetyl)pyrrolidinyl-3-oxy]-2-fluoro-4-aminobenzene in 75 mL 2:1 acetone:H₂O at 0°C was added 527 mg (6.27 mmol) NaHCO₃ and 0.88 mL (2.56 mmol) Cbz-Cl. The reaction was allowed to warm to rt and stirred overnight. The volatiles were evaporated, the residue diluted with 200 mL H₂O and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with H₂O, dried over MgSO₄, filtered, and the solvent removed by rotary evaporation. Silica gel chromatography (EtOAc) afforded 473 mg (38%) of 3-fluoro-4-[N-(benzyloxyacetyl)pyrrolidinyl-3-oxy]-1-(phenylmethoxycarbonylamino); MS (CI) [M+H]⁺ 479.

(R)-[3-[3-Fluoro-4-(N-(benzyloxyacetyl)pyrrolidinyl-3-oxy)phenyl]-2-oxo-5-oxazolidinyl]methanol:

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To 473 mg (0.99 mmol) of 2-fluoro-1-(N-(benzyloxyacetyl)pyrrolidinyl-3-oxy)-4-(phenylmethoxycarbonylamino)benzene in 25 mL dry THF at -78°C was added 0.55 mL (1.38 mmol) 2.5M *n*-BuLi and the reaction warmed to rt and stirred for 1 h. Then the solution was again cooled to -78°C and 0.19 mL (1.38 mmol) (R)-glycidyl butyrate was added via syringe and the reaction warmed to rt and stirred overnight. The reaction was carefully poured into 50 mL sat. NH_4Cl (aq.) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with H_2O , dried over MgSO_4 , filtered, and the solvent removed by rotary evaporation. Silica gel chromatography (0% to 10% MeOH in EtOAc) gave 107 mg (25%) of (R)-[3-[3-Fluoro-4-(N-(benzyloxyacetyl)pyrrolidinyl-3-oxy)phenyl]-2-oxo-5-oxazolidinyl]methanol as a gold oil; MS (CI) $[\text{M}+\text{Na}]^+$ 445.

(R)-[3-[3-Fluoro-4-(N-(benzyloxyacetyl)pyrrolidinyl-3-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl methanesulfonate:

To 107 mg (0.24 mmol) of (R)-[3-[3-fluoro-4-(N-(benzyloxyacetyl)pyrrolidinyl-3-oxy)phenyl]-2-oxo-5-oxazolidinyl]methanol in 50 mL CH_2Cl_2 at 0°C was added 0.07 mL (0.48 mmol) NEt_3 and 0.03 mL (0.34 mmol) methanesulfonyl chloride. After warming to rt and stirring for 1 h the reaction was diluted with 10 mL CH_2Cl_2 , washed with H_2O , dried over MgSO_4 , filtered and the solvent removed by rotary evaporation to yield (R)-[3-[3-fluoro-4-(N-(benzyloxyacetyl)pyrrolidinyl-3-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl methanesulfonate; MS (CI) $[\text{M}+\text{H}]^+$ 523.

(R)-[3-[3-Fluoro-4-(N-(benzyloxyacetyl)pyrrolidinyl-3-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyldiazide:

To a solution of 2.22 g (4.25 mmol) of (R)-[3-[3-fluoro-4-(N-(benzyloxyacetyl)pyrrolidinyl-3-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl methanesulfonate in 40 mL DMF was added 1.05 g (16.13 mmol) sodium azide and the reaction heated at 75°C overnight. Then the reaction was poured into 20 mL H_2O and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with H_2O , dried over Na_2SO_4 , filtered, and the solvent removed by rotary evaporation to yield 1.29 g (65%) of (R)-[3-[3-Fluoro-4-(N-(benzyloxyacetyl)pyrrolidinyl-3-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyldiazide; MS (CI) $[\text{M}+\text{H}]^+$ 471.

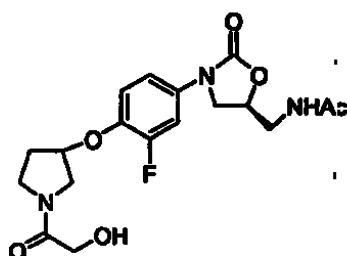
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(S)-N-[[3-[3-Fluoro-4-{N-(benzyloxyacetyl)pyrrolidinyl-3-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide (Compound 39):

To a solution of 1.29 g (2.74 mmol) of (R)-[3-[3-fluoro-4-{N-(benzyloxyacetyl)pyrrolidinyl-3-oxy}phenyl]-2-oxo-5-oxazolidinyl]methylazide in 30 mL MeOH was added 1.38 mL (13.71 mmol) 1,3-propanedithiol and 1.91 mL (13.71 mmol) NEt₃ and the reaction stirred overnight at rt. Then 0.78 mL (8.23 mmol) acetic anhydride and 1.33 mL (16.45 mmol) pyridine were added and the reaction stirred at rt for 3 h. The reaction was filtered through a fritted funnel, rinsed with MeOH, and concentrated under reduced pressure. Then the residue was diluted with EtOAc, washed with H₂O (3 x 100 mL), washed with brine, dried over Na₂SO₄, and the solvent removed under reduced pressure to give an orange oil. Purification by silica gel chromatography (10% MeOH in EtOAc) gave 1.02 g (77%) of (S)-N-[[3-[3-fluoro-4-{N-(benzyloxyacetyl)pyrrolidinyl-3-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide as a white foam; mp 53-55°C, MS (CI) [M+H]⁺ 486.

Example 40

(S)-N-[[3-[3-Fluoro-4-{N-(α-hydroxyacetyl)pyrrolidinyl-3-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide



Compound 40

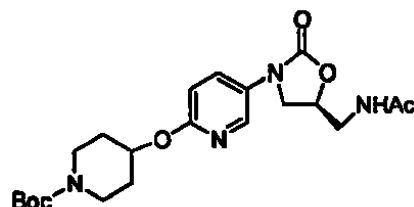
To a solution of 695 mg (1.43 mmol) of Compound 39 in 40 mL MeOH was added 451 mg (7.17 mmol) ammonium formate and a catalytic amount of 10% Pd/C, and the reaction was heated at reflux overnight. Then the reaction was filtered through a pad of celite and the solvent removed under reduced pressure. Trituration with EtOAc, MeOH, and hexanes afforded 363 mg (64%) of (S)-N-[[3-[3-fluoro-4-{N-(α-hydroxyacetyl)pyrrolidinyl-3-oxy}phenyl]-2-oxo-5-

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oxazolidinyl)methyl]acetamide as a white powder; mp 97-99°C; MS (CI) [M+H]⁺ 396.

Example 41

5 (5S)-3-[6-{N-(*t*-Butoxycarbonyl)piperidinyl-4-oxy}-pyridin-3-yl]-5-methylacetamide-oxazolidin-2-one



Compound 41

10 2-[N-(*t*-Butoxycarbonyl)piperidinyl-4-oxy]-5-nitropyridine:

To a solution of 15.23 g (75.7 mmol) N-(*t*-butoxycarbonyl)-4-piperidinol in 450 mL THF at 0°C was added 126 mL (126 mmol) KO^tBu and the reaction stirred for 40 min. Then 10.0 g (63 mmol) 2-chloro-5-nitropyridine was added and the reaction warmed to rt and stirred overnight. The reaction was diluted with H₂O, extracted with Et₂O, dried over MgSO₄, filtered, and the solvent removed under reduced pressure to yield the crude product as a black oil. Purification by silica gel chromatography (1:1 EtOAc:hexanes) gave the desired product; MS (CI) [M+H]⁺ 324.

20 2-[N-(*t*-Butoxycarbonyl)piperidinyl-4-oxy]-5-aminopyridine:

A solution of 280 mg (0.87 mmol) of 2-[N-(*t*-butoxycarbonyl)piperidinyl-4-oxy]-5-nitropyridine in 30 mL of EtOH was treated with a catalytic amount of 10% Pd/C, followed by hydrogenation at 50 psi overnight. The suspension was filtered through celite and the filtrate evaporated under reduced pressure to afford crude amine as a dark solid; MS (CI) [M+H]⁺ 294.

25 2-[N-(*t*-Butoxycarbonyl)piperidinyl-4-oxy]-5-(phenylmethoxycarbonylamino)pyridine:

To a solution of 5.4 g (18.4 mmol) of 2-[N-(*t*-butoxycarbonyl)piperidinyl-4-oxy]-5-aminopyridine in 300 mL 1:1 THF:H₂O was added 7.18 g (22.1 mmol)

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cesium carbonate and 3.16 mL (22.1 mmol) benzylchloroformate and the reaction stirred at rt overnight. The mixture was diluted with H₂O, extracted with EtOAc, dried over MgSO₄, filtered, and the solvent removed under reduced pressure to give a dark solid. Purification by silica gel chromatography (4:1 hexanes:EtOAc) yielded 6.5 g (83%) of the carbamate as a yellow solid; MS (CI) [M+H]⁺ 428.

(R)-[3-[6-(N-(t-Butoxycarbonyl)piperdiny-4-oxy)pyridin-3-yl]-2-oxo-5-oxazolidinyl]methanol:

A solution of 5.17 g (12.1 mmol) of 2-(N-(t-butoxycarbonyl)piperdiny-4-oxy)-5-(phenylmethoxy carbonylamino)pyridine in 250 mL THF was cooled to -78°C and 5.32 mL (13.3 mmol) 2.5 M nBuLi was added and the solution stirred for 1 h. Then 1.89 mL (13.3 mmol) R-glycidyl butyrate was added and the reaction allowed to warm to rt and stirred overnight. The reaction was quenched with H₂O, extracted with Et₂O, dried over MgSO₄, filtered, and the solvent removed under reduced pressure to yield 4.22 g (88%) of the alcohol as a brown oil; MS (CI) [M+H]⁺ 394.

(R)-[3-[4-(N-(t-Butoxycarbonyl)piperdiny-4-oxy)pyridin-3-yl]-2-oxo-5-oxazolidinyl]methylmethanesulfonate:

To a solution of 4.22 g (10.7 mmol) of (R)-[3-[6-(N-(t-butoxycarbonyl)piperdiny-4-oxy)pyridin-3-yl]-2-oxo-5-oxazolidinyl]methanol in 100 mL CH₂Cl₂ at 0°C was added 2.99 mL (21.4 mmol) NEt₃ and the reaction stirred for 45 min. Then 1.16 mL (15.0 mmol) methanesulfonylchloride was added and the reaction stirred at rt overnight. The reaction was quenched with H₂O, extracted with CH₂Cl₂, dried over MgSO₄, filtered, and the solvent removed under reduced pressure to yield the mesylate as a brown solid.

(R)-[3-[4-(N-(t-Butoxycarbonyl)piperdiny-4-oxy)pyridin-3-yl]-2-oxo-5-oxazolidinyl]methylazide:

To a solution of (R)-[3-[6-(N-(t-butoxycarbonyl)piperdiny-4-oxy)pyrid-3-yl]-2-oxo-5-oxazolidinyl]methylmethanesulfonate (10.7 mmol) in 100 mL DMF was added 2.78 g (42.8 mmol) sodium azide and the reaction heated at 75°C for 5 h. The reaction was cooled and the solvent removed under reduced pressure. The

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residue was diluted with H₂O, extracted with EtOAc, dried over MgSO₄, filtered, and the solvent removed under reduced pressure to yield a brown oil which was used crude in the next reaction.

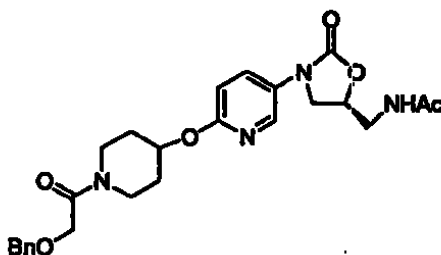
5 (5S)-3-[6-{N-(*t*-Butoxycarbonyl)piperidinyl-4-oxy}-pyridin-3-yl]-5-methylacetamide-oxazolidin-2-one (Compound 41):

A solution of 3.3 g (7.9 mmol) of (R)-[3-[6-{N-(*t*-butoxycarbonyl)piperidinyl-4-oxy}pyridin-3-yl]-2-oxo-5-oxazolidinyl]methylazide in 30 mL of EtOAc was treated with a catalytic amount of 10% Pd/C, followed by hydrogenation at 50 psi

10 overnight. The suspension was filtered through celite and the filtrate evaporated under reduced pressure to afford crude amine as a dark solid. The crude reaction mixture was treated with 0.47 mL (5.8 mmol) pyridine and 2.39 mL (25 mmol) acetic anhydride and stirred overnight at rt. The volatiles were removed under reduced pressure to give a brown oil. Purification by silica gel chromatography (5% MeOH in EtOAc) yielded 1.7 g of (5S)-3-[6-{N-(*t*-butoxycarbonyl)piperidinyl-4-oxy}-pyridin-3-yl]-5-methylacetamide-oxazolidin-2-one as a white foam; mp 99-101°C, MS (CI)[M+H]⁺ 435.

Example 42

(5S)-3-[6-{N-(Benzyloxyacetyl)piperidinyl-4-oxy}-pyridin-3-yl]-5-methylacetamide-oxazolidin-2-one



Compound 42

25 (S)-3-[6-{N-(Piperidinyl-4-oxy)pyridin-3-yl]-2-oxo-5-oxazolidinyl] methyl]acetamide:

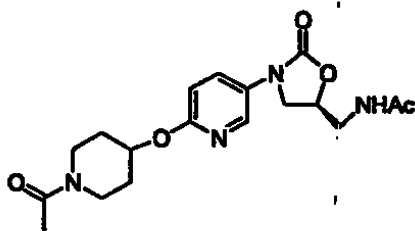
To a solution of 500 mg (1.1 mmol) of Compound 41 in 50 mL CH₂Cl₂ was added 0.88 mL (11.2 mmol) trifluoroacetic acid and the reaction stirred at rt for 3 days. The volatiles were removed under reduced pressure to give the TFA salt as a brown oil.

(5S)-3-[6-{N-(Benzyloxyacetyl)piperidinyl-4-oxy}-pyridin-3-yl]-5-methylacetamide-oxazolidin-2-one (Compound 42):

A solution of 99 mg (0.18 mmol) of (R)-3-[6-{N-(piperidinyl-4-oxy)pyridin-3-yl}-2-oxo-5-oxazolidinyl] methyl]acetamide in 20 mL CH₂Cl₂ was treated with 0.12 mL (0.88 mmol) NEt₃ and the reaction stirred at rt for 30 min. Then 0.06 mL (0.36 mmol) benzyloxyacetylchloride was added and the reaction stirred overnight. Then 100 mg of PS-Trisamine was added and the suspension stirred for 30 min. The reaction was filtered, quenched with 10 mL H₂O, extracted with CH₂Cl₂ (2 x 20 mL), dried over MgSO₄, and the solvent removed by rotary evaporation to give 31 mg of (5S)-3-[6-{N-(benzyloxyacetyl)piperidinyl-4-oxy}-pyridin-3-yl]-5-methylacetamide-oxazolidin-2-one as a tan semi-solid. ¹H NMR (CDCl₃) δ 8.13 (s, 1H); 7.98 (m, 1H); 7.35 (m, 5H); 6.72 (m, 1H); 6.59 (m, 1H); 5.25 (m, 1H); 4.82 (m, 1H); 4.61 (s, 2H); 4.24 (s, 2H); 3.90 (m, 1H); 3.77 (m, 2H); 3.70 (m, 1H); 3.68 (m, 2H); 3.54 (m, 1H); 3.41 (m, 1H); 2.08 (s, 3H); 2.05 (m, 2H); and 1.83 (m, 2H).

Example 43

(5S)-3-[6-{N-(Acetyl)piperidinyl-4-oxy}-pyridin-3-yl]-5-methylacetamide-oxazolidin-2-one



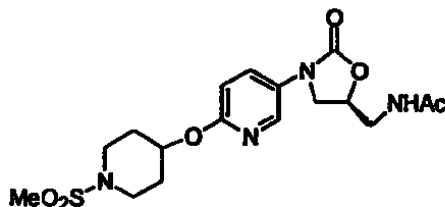
Compound 43

Compound 43 was prepared from 71 mg (0.13 mmol) of the TFA salt from Example 42, 0.09 mL (0.63 mmol) NEt₃, and 0.02 mL (0.26 mmol) acetyl chloride as described above to give 20 mg of (5S)-3-[6-{N-(acetyl)piperidinyl-4-oxy}-pyridin-3-yl]-5-methylacetamide-oxazolidin-2-one as a white semi-solid. ¹H NMR (CDCl₃) δ 8.14 (m, 1H); 7.95 (m, 1H); 6.77 (s, 1H); 6.76 (brs, 1H); 5.25 (m, 1H); 4.83 (m, 1H); 4.06 (m, 1H); 3.91 (m, 1H); 3.80 (m, 1H); 3.68 (m, 3H); 3.4-3.6 (m, 2H); 2.15 (s, 3H); 2.04 (s, 3H); 2.02 (m, 2H); and 1.77 (m, 2H).

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Example 44

(5S)-3-[6-{N-(Methanesulfonyl)piperidin-4-yl}-pyridin-3-yl]-
5-methylacetamide-oxazolidin-2-one



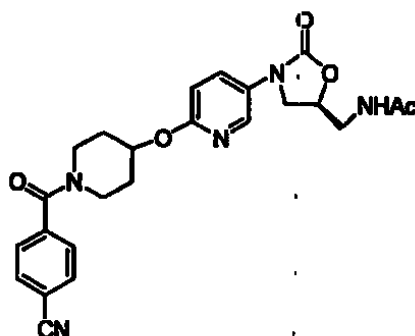
Compound 44

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Compound 44 was prepared from 56 mg (0.10 mmol) of the TFA salt from Example 42, 0.07 mL (0.50 mmol) NEt_3 , and 0.02 mL (0.20 mmol) methanesulfonyl chloride as described above to give 17 mg of (5S)-3-[6-{N-(methanesulfonyl)piperidin-4-yl}-pyridin-3-yl]-5-methylacetamide-oxazolidin-2-one as a white solid; mp 175-176°C, MS (CI) $[\text{M}+\text{H}]^+$ 413.

Example 45

(5S)-3-[6-{N-(4-Cyanobenzoyl)piperidin-4-yl}-pyridin-3-yl]-
5-methylacetamide-oxazolidin-2-one



Compound 45

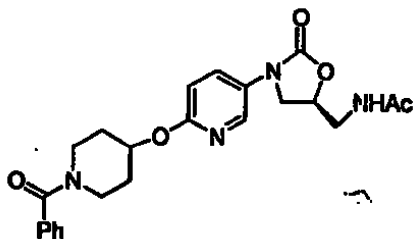
Compound 45 was prepared from 39 mg (0.07 mmol) of the TFA salt from Example 42, 0.05 mL (0.35 mmol) NEt_3 , and 23 mg (0.14 mmol) 4-cyanobenzoyl chloride as described above to give 30 mg of (5S)-3-[6-{N-(4-cyanobenzoyl)piperidin-4-yl}-pyridin-3-yl]-5-methylacetamide-oxazolidin-2-one as a white semi-solid. ^1H NMR (CDCl_3) δ 8.13 (m, 1H); 7.97 (m, 1H); 7.69 (m, 2H); 7.57 (m,

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2H); 6.78 (m, 1H); 6.48 (br t, 1H); 5.34 (m, 1H); 4.82 (m, 1H); 4.18 (m, 2H); 3.5-3.8 (m, 5H); 3.37 (m, 1H); 2.03 (s, 3H); 1.97 (m, 2H); and 1.82 (m, 2H).

Example 46

(5S)-3-[6-[N-(Benzoyl)piperidiny-4-oxy]-pyridin-3-yl]-5-methylacetamide-oxazolidin-2-one

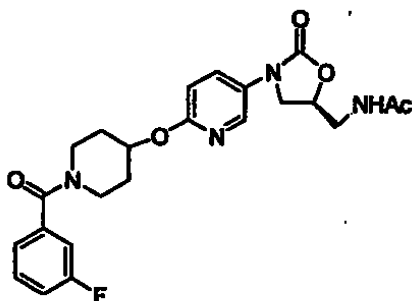


Compound 46

Compound 46 was prepared from 48 mg (0.09 mmol) of the TFA salt from Example 42, 0.06 mL (0.43 mmol) NEt_3 , and 0.02 mL (0.20 mmol) benzoyl chloride as described above to give 50 mg of (5S)-3-[6-[N-(benzoyl)piperidiny-4-oxy]-pyridin-3-yl]-5-methylacetamide-oxazolidin-2-one as a yellow solid; mp 180-182°C, MS (CI) $[M+H]^+$ 439.

Example 47

(5S)-3-[6-[N-(3-Fluorobenzoyl)piperidiny-4-oxy]-pyridin-3-yl]-5-methylacetamide-oxazolidin-2-one



Compound 47

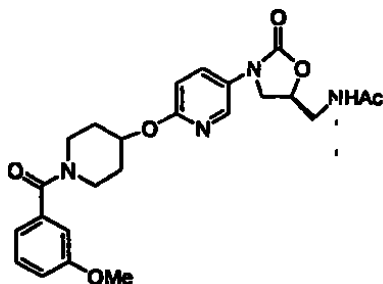
Compound 47 was prepared from 50 mg (0.12 mmol) of the TFA salt from Example 42, 0.08 mL (0.60 mmol) NEt_3 , and 0.03 mL (0.24 mmol) 3-fluorobenzoyl chloride as described above to give 20 mg of (5S)-3-[6-[N-(3-

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fluorobenzoyl)piperidiny-4-oxy-pyridin-3-yl]-5-methylacetamid-oxazolidin-2-one as a clear oil; MS (CI) $[M+H]^+$ 457.

Example 48

5 (5S)-3-[6-{N-(3-Methoxybenzoyl)piperidiny-4-oxy}-pyridin-3-yl]-5-methylacetamide-oxazolidin-2-one

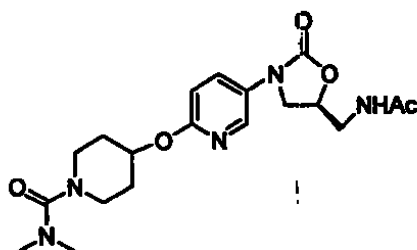


Compound 48

Compound 48 was prepared from 50 mg (0.12 mmol) of the TFA salt from Example 42, 0.08 mL (0.60 mmol) NEt_3 , and 0.03 mL (0.24 mmol) 3-methoxybenzoyl chloride as described above to give 20 mg of (5S)-3-[6-{N-(3-methoxybenzoyl)piperidiny-4-oxy}-pyridin-3-yl]-5-methylacetamide-oxazolidin-2-one as a yellow oil; MS (CI) $[M+H]^+$ 468.

Example 49

(5S)-3-[6-{N-(Dimethylcarbamoyl)piperidiny-4-oxy}-pyridin-3-yl]-5-methylacetamide-oxazolidin-2-one



Compound 49

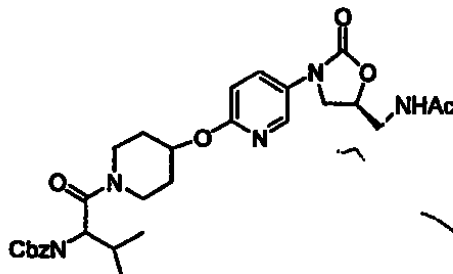
Compound 49 was prepared from 50 mg (0.12 mmol) of the TFA salt from Example 42, 0.08 mL (0.60 mmol) NEt_3 , and 0.02 mL (0.24 mmol) dimethylcarbamoyl chloride as described above to give 17 mg of (5S)-3-[6-{N-

299.24

(dimethylcarbamoyl) piperidinyl-4-oxy-pyridin-3-yl]-5-methylacetamide-oxazolidin-2-one as a white semi-solid; MS (CI) [M+H]⁺ 406.

Example 50

- 5 (5S)-3-[6-{N-(2-Benzoyloxycarbonyl-3-methylbutyryl)piperidinyl-4-oxy}-pyridin-3-yl]-5-methylacetamide-oxazolidin-2-one



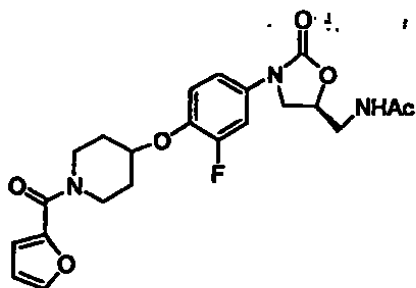
Compound 50

To a solution of 36 mg (0.06 mmol) of the TFA salt from Example 42 in 20 mL CH₂Cl₂ was added 32 mg (0.13 mmol) Cbz-VAL-OH, 13 mg (0.07 mmol) EDCI, and 35 mg (0.25 mmol) HOBt. The reaction stirred at rt overnight. Then the solution was washed with H₂O, extracted with CH₂Cl₂, washed with sat. NaHCO₃, dried with MgSO₄, and concentrated to give 10 mg of (5S)-3-[6-{N-(2-Benzoyloxycarbonyl-3-methylbutyryl)piperidinyl-4-oxy}-pyridin-3-yl]-5-methylacetamide-oxazolidin-2-one as a clear oil. ¹H NMR (CDCl₃) δ 8.10 (m, 1H); 7.99 (m, 1H); 7.37 (m, 5H); 6.76 (m, 1H); 6.20 (m, 1H); 5.33 (s, 2H); 5.19 (m, 1H); 5.11 (m, 1H); 4.82 (m, 1H); 4.08 (m, 1H); 3.79 (m, 2H); 3.5-3.7 (m, 4H); 3.25 (m, 1H); 2.97 (m, 1H); 2.13 (m, 2H); 2.06 (s, 3H); 1.84 (m, 2H); and 1.30 (s, 6H).

Example 51

(S)-N-[[3-[3-Fluoro-4-(N-(2-furoyl)piperidinyl-4-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

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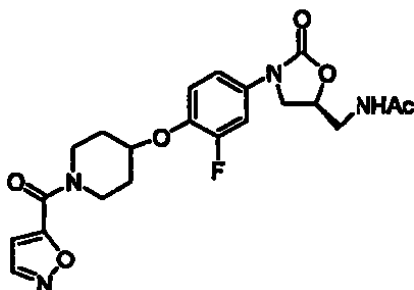


Compound 51

To a solution of 572 mg TFA salt in Example 2 in 50 mL CH_2Cl_2 , was added 1.2 mL triethylamine (TEA) and 0.20 mL 2-furanoyl chloride. The reaction was stirred for 18 hours under a nitrogen atmosphere. The reaction was poured into 100 mL water and extracted. The organic layer was dried over MgSO_4 , filtered and evaporated to an oil. This was triturated with warm ether to afford (S)-N-[[3-[3-fluoro-4-{N-(2-furoyl)piperidin-4-yl}oxy]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide as a white solid; mp=134-136 °C; MS (CI) $[\text{M}+\text{H}]^+$ 446.

Example 52

(S)-N-[[3-[3-Fluoro-4-{N-(5-isoxazolylcarbonyl)piperidin-4-yl}oxy]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide



Compound 52

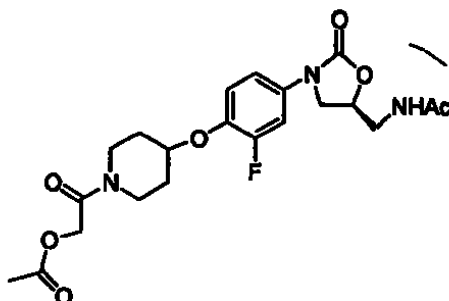
To 433 mg (3.83 mmoles) of 5-isoxazole carboxylic acid in 10 mL CH_2Cl_2 , was added 1 drop of DMF followed by 2 mL oxalyl chloride (2M in CH_2Cl_2 ; 4 mmoles). After stirring for 0.5 hour, a solution of 895 mg (1.92 mmoles) TFA salt in Example 2 and 1 mL of TEA in 5 mL CH_2Cl_2 was added. The reaction was dried over MgSO_4 , filtered and evaporated. This was purified by column chromatography with 5% MeOH/ CH_2Cl_2 as the eluant to afford (S)-N-[[3-[3-fluoro-

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4-[N-(5-isoxazolylcarbonyl)piperdiny-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide as a white foam. ¹H NMR (CDCl₃) δ 8.31 (d, J=1.8 Hz, 1H), 7.49 (dd, J=12.9, 2.6 Hz, 1H), 7.08-7.12 (m, 1H), 7.01 (t, J=8.8 Hz, 1H), 6.77 (d, J=1.8 Hz, 1H), 6.04 (t, J=6.0 Hz, 1H), 4.73-4.81 (m, 1H), 4.52-4.57 (m, 1H), 4.03 (t, J=9.0 Hz, 1H), 3.56-3.95 (m, 7H), 2.03 (s, 3H), 1.75-2.00 (m, 4H). MS (CI) [M+H]⁺ 447.

Example 53

(S)-N-[[3-[3-Fluoro-4-{N-(acetoxycacetyl)piperidiny-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide



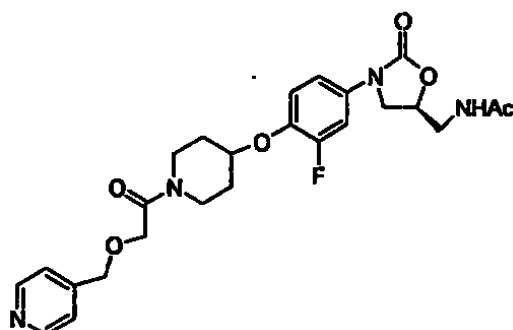
Compound 53

To 2.12 g (4.55 mmol) of TFA salt of Example 2 in 150 mL CH₂Cl₂, was added 5 mL TEA. After stirring for 15 min, 0.62 (5.76 mmol) acetoxycacetyl chloride was added and the reaction stirred for 2.5 h. The volatiles were evaporated and the residue chromatographed using 10% MeOH/ CH₂Cl₂ as the eluant. (S)-N-[[3-[3-Fluoro-4-{N-(acetoxycacetyl)piperidiny-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide was isolated as a pale beige solid; mp=146-147.5°C, MS (CI) [M+H]⁺ 452.

Example 54

(S)-N-[[3-[4-{N-(Pyridin-4-ylmethoxyacetyl)piperidiny-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

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Compound 54

(S)-N-[[3-[4-(N-(Chloroacetyl)piperidin-4-yl)oxy]phenyl]-2-oxo-5-oxazolidinyl]methylacetamide:

A solution of 4.19 g (9.00 mmol) of TFA salt of Example 2 and 3 mL of TEA in 125 mL CH_2Cl_2 was added dropwise to 0.75 mL of chloroacetylchloride (9.42 mmol) in 100 mL CH_2Cl_2 . After stirring at room temperature for 2 h, the reaction was poured into 300 mL water and extracted. The organic layer was dried over MgSO_4 , filtered and evaporated to give (S)-N-[[3-[4-(N-(Chloroacetyl)piperidin-4-yl)oxy]phenyl]-2-oxo-5-oxazolidinyl]methylacetamide as a viscous oil.

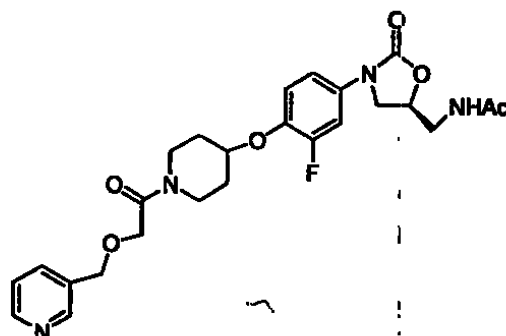
(S)-N-[[3-[4-(N-(Pyridin-4-ylmethoxyacetyl)piperidin-4-yl)oxy]phenyl]-2-oxo-5-oxazolidinyl]methylacetamide (Compound 54):

To 101.1 mg NaH (60% in oil; 2.53 mmol) in 5 mL anhyd THF at 0°C , was added dropwise 265 mg (2.43 mmol) pyridine-4-methanol in 5 mL anhyd THF. After stirring for 15 min, 503 mg (1.18 mmol) (S)-N-[[3-[4-(N-(chloroacetyl)piperidin-4-yl)oxy]phenyl]-2-oxo-5-oxazolidinyl]methylacetamide in 5 mL anhyd THF was added. The reaction was stirred at room temperature for 16 h, and then poured into 125 mL water. This was extracted with 3 x 100 mL CH_2Cl_2 . The combined organic layers were dried over MgSO_4 , filtered and evaporated. Pure (S)-N-[[3-[4-(N-(pyridin-4-ylmethoxyacetyl)piperidin-4-yl)oxy]phenyl]-2-oxo-5-oxazolidinyl]methylacetamide, obtained by chromatography using 5% MeOH/ CH_2Cl_2 , was isolated as a white foam. ^1H NMR (CDCl_3) δ 8.59 (d, $J=5.9$ Hz, 2H), 7.47 (dd, $J=12.9, 2.6$ Hz, 1H), 7.28 (d, $J=5.9$ Hz, 2H), 7.07-7.11 (m, 1H), 6.99 (t, $J=8.8$ Hz, 1H), 5.91-5.94 (m, 1H), 4.72-4.79 (m, 1H), 4.65 (s, 2H), 4.45-4.49 (m, 1H), 4.26 (s, 2H), 4.02 (t, $J=8.9$ Hz, 1H), 3.40-3.78 (m, 7H), 2.02 (s, 3H), 1.85-1.95 (m, 4H). MS (CI) $[\text{M}+\text{H}]^+$ 501.

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Example 55

(S)-N-[[3-[4-{N-(Pyridin-3-ylmethoxyacetyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methylacetamide



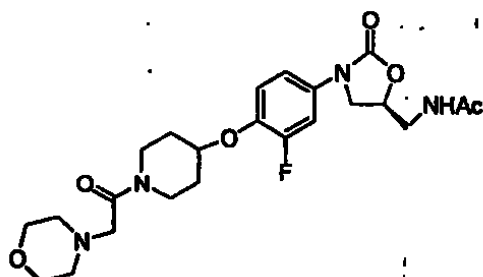
Compound 55

To 117 mg NaH (60% in oil; 2.93 mmol) in 5 mL anh THF at 0°C, was added dropwise 0.24 mL (2.47 mmol) pyridine-3-methanol in 5 mL THF. After stirring for 15 minutes, 523 mg (1.22 mmol) chloroacetamide from Example 54 in 5 mL anh THF was added in one portion. The reaction was warmed to room temperature and stirred for 72 hours. The reaction was poured into 50 mL water and extracted 3 x 75 mL CH₂Cl₂. The combined organic layers were dried over MgSO₄, filtered and evaporated. Chromatography with 3% MeOH/CH₂Cl₂ afforded (S)-N-[[3-[4-{N-(pyridin-3-ylmethoxyacetyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methylacetamide as a clear glass. ¹H NMR (CDCl₃) δ 8.56-8.60 (m, 2H), 7.73 (d, J=7.8 Hz, 1H), 7.47 (dd, J=13.0, 2.6 Hz, 1H), 7.30 (dd, J=7.8, 5.1 Hz, 1H), 7.08 (dd, J=8.9, 1.6 Hz, 1H), 6.99 (t, J=8.9 Hz, 1H), 6.02 (t, J=6.2 Hz, 1H), 4.70-4.78 (m, 1H), 4.64 (s, 2H), 4.43-4.47 (m, 1H), 4.24 (s, 2H), 4.02 (t, J=8.9 Hz, 1H), 3.57-3.78 (m, 6H), 3.35-3.45 (m, 1H), 2.02 (s, 3H), 1.80-1.96 (m, 4H). MS (CI) [M+H]⁺ 501.

Example 56

(S)-N-[[3-[4-{N-(Morpholinoacetyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methylacetamide

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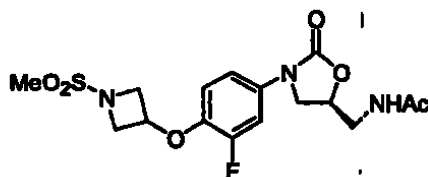


Compound 56

To 415 mg (0.97 mmol) of chloroacetamide from Example 54 in 15 mL THF, was added 0.25 mL (2.87 mmol) morpholine. The reaction was stirred for 72 hours at room temperature, poured into 50 mL water and extracted 3 x 50 mL CH₂Cl₂. The combined organic layers were washed with water, dried over MgSO₄, filtered and evaporated. (S)-N-[[3-[4-(N-Morpholinoacetyl)-piperidin-4-oxo]phenyl]-2-oxo-5-oxazolidinyl]methylacetamide was obtained as a clear glass after chromatography (3% MeOH/CH₂Cl₂). ¹H NMR (CDCl₃) δ 7.47 (dd, J=13.0, 2.6 Hz, 1H), 7.07-7.11 (m, 1H), 7.00 (t, J=8.8 Hz, 1H), 5.93 (br t, J=6.1 Hz, 1H), 4.73-4.79 (m, 1H), 4.44-4.78 (m, 1H), 4.02 (t, J=9.0 Hz, 1H), 3.51-3.85 (m, 11H), 3.20 (s, 2H), 2.47-2.51 (m, 4H), 2.03 (s, 3H), 1.81-1.96 (m, 4H). MS (CI) [M+H]⁺ 479.

Example 57

(S)-N-[[3-[3-Fluoro-4-(N-(methanesulfonyl)azetidiny-3-oxo]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide



Compound 57

1-[N-(Diphenylmethyl)azetidiny-3-oxo]-2-fluoro-4-nitrobenzene:

To 5.40 g (22.56 mmol) N-(diphenylmethyl)azetidin-4-ol in 200 mL THF at 0°C, was added 30 mL KOtBu (1M in THF; 30 mmol). After stirring for 0.5 h, 2.5 mL (22.58 mmol) 3,4-difluoronitrobenzene was added. The reaction was warmed to room temperature and stirred for 18 h. After evaporation of the THF, the

residue was partitioned between 300 mL water and 250 mL CH_2Cl_2 . The aqueous was washed with additional CH_2Cl_2 . The combined organic layers were dried over MgSO_4 , filtered and evaporated. Chromatography with 15% EtOAc/hexanes afforded pure 1-[N-(Diphenylmethyl)azetidiny-4-oxy]-2-fluoro-4-nitrobenzene as a viscous gold oil. ^1H NMR (CDCl_3) δ 7.96-8.01 (m, 2H), 7.16-7.47 (m, 10H), 6.72-6.80 (m, 1H), 4.88-5.00 (m, 1H), 4.94 (s, 1H), 3.70-3.81 (m, 2H), 3.17-3.27 (m, 2H). MS (CI) $[\text{M}+\text{H}]^+$ 379.

1-[N-(Diphenylmethyl)azetidiny-3-oxy]-2-fluoro-4-aminobenzene:

7.55 g (19.95 mmol) 1-[N-(diphenylmethyl)azetidiny-4-oxy]-2-fluoro-4-nitrobenzene, 7.31 g (116 mmol) ammonium formate, and approximately 250 mg 10% Pd/C in 500 mL MeOH were heated at reflux for 21 h. After cooling, the reaction was filtered through a pad of Celite and the methanol evaporated to afford crude 1-[N-(diphenylmethyl)azetidiny-4-oxy]-2-fluoro-4-aminobenzene as a mustard yellow semisolid. ^1H NMR (CDCl_3) δ 7.13-7.48 (m, 10H), 6.57 (t, $J=8.8$ Hz, 1H), 6.43 (dd, $J=12.9, 2.6$ Hz, 1H), 6.23-6.30 (m, 1H), 4.67-4.80 (m, 1H), 4.52 (s, 1H), 4.00 (br s, 2H), 3.73-3.85 (m, 2H), 3.13-3.23 (m, 2H). MS (CI) $[\text{M}+\text{H}]^+$ 349.

2-Fluoro-1-[N-(diphenylmethyl)azetidiny-3-oxy]-4-(benzyloxycarbonylamino)-benzene:

Crude aniline (6.19 g; 17.77 mmol) in 750 mL of acetone/water (2:1) was cooled to 0°C . 3.34 g (39.76 mmol) sodium bicarbonate was added followed by 3.3 mL (23.39 mmol) benzylchloroformate. The reaction was stirred at room temperature for 20 h and the volatiles were evaporated. The aqueous residue was extracted 3 x 250 mL EtOAc. The combined organic layers were dried over MgSO_4 , filtered and evaporated. Chromatography with 50% EtOAc/hexanes afforded pure 2-fluoro-1-[N-(diphenylmethyl)azetidiny-3-oxy]-4-(benzyloxycarbonylamino)benzene as a white solid; mp= $128-131^\circ\text{C}$; MS (CI) $[\text{M}+\text{H}]^+$ 483.

(R)-[3-[3-Fluoro-4-[N-(diphenylmethyl)azetidiny-3-oxy]phenyl]-2-oxo-5-oxazolidinyl]methanol:

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To 2.13 g (4.41 mmol) of 2-fluoro-1-{N-(diphenylmethyl)azetidiny-3-oxy}-4-(benzyloxycarbonylamino)benzene in 75 mL of THF at -78°C under a nitrogen atmosphere, was added 2.5 mL nBuLi (2.5 M in hexanes; 6.25 mmol). The reaction was stirred for 0.5 h and then 0.65 mL of (R)-glycidyl butyrate (4.59 mmol) was added. The reaction was stirred at room temperature overnight, poured into 75 mL of saturated ammonium chloride (aq) and extracted 3 x 100 mL EtOAc. The combined organic layers were washed with water, dried over MgSO₄, filtered and evaporated. Chromatography with 60% EtOAc/hexanes afforded (R)-[3-[3-Fluoro-4-{N-(diphenylmethyl)azetidiny-3-oxy}phenyl]-2-oxo-5-oxazolidiny]methanol as an off-white foam. ¹H NMR (CDCl₃) δ 7.17-7.51 (m, 11H), 7.03 (d, J=8.9 Hz, 1H), 6.70 (t, J=8.9 Hz, 1H), 4.70-4.90 (m, 2H), 4.44 (s, 1H), 3.87-4.13 (m, 3H), 3.68-3.76 (m, 3H), 3.13-3.18 (m, 2H), 2.05 (br t, 1H). MS (CI) [M+H]⁺ 449.

(S)-[3-[3-Fluoro-4-{N-(diphenylmethyl)azetidiny-3-oxy}phenyl]-2-oxo-5-oxazolidiny]methyl azide:

To 1.40 g (3.12 mmol) of (R)-[3-[3-fluoro-4-{N-(diphenylmethyl)-azetidiny-3-oxy}phenyl]-2-oxo-5-oxazolidiny]methanol and 0.90 mL (6.46 mmol) TEA in 90 mL CH₂Cl₂ at 0°C under a nitrogen atmosphere, was added 0.3 mL (3.87 mmol) methanesulfonyl chloride. After stirring for 1.5 h, the reaction was poured into 150 mL water and extracted. The aqueous layer was washed with an additional portion of CH₂Cl₂. The combined organic layers were dried over MgSO₄, filtered and evaporated to give crude mesylate. MS (CI) [M+H]⁺ 527. This mesylate (3.08 mmol) and 0.80 g (12.31 mmol) sodium azide in 75 mL DMF were heated at 70°C for 2.5 hours under a nitrogen atmosphere. After cooling, the reaction was poured into 400 mL water and extracted 3 x 150 mL EtOAc. The combined organic layers were washed with several portions of water, dried over MgSO₄, filtered and evaporated to yield (R)-[3-[3-fluoro-4-{N-(diphenylmethyl)azetidiny-3-oxy}phenyl]-2-oxo-5-oxazolidiny]methyl azide as a semi-solid. ¹H NMR (CDCl₃) δ 7.19-7.50 (m, 11H), 7.05 (d, J=9.0 Hz, 1H), 6.74 (t, J=9.0 Hz, 1H), 4.71-4.87 (m, 2H), 4.46 (s, 1H), 4.03 (t, J=8.8 Hz, 1H), 3.50-3.88 (m, 5H), 3.10-3.21 (m, 2H). MS [M+H]⁺ 474.

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(S)-[3-[3-Fluoro-4-(N-(diphenylmethyl)azetidiny-3-oxy)phenyl]-2-oxo-5-oxazolidiny]methylacetamide:

5 1.13 g (2.39 mmol) (R)-[3-[3-Fluoro-4-(N-(diphenylmethyl)azetidiny-3-oxy)phenyl]-2-oxo-5-oxazolidiny]methyl azide and 0.85 g (3.24 mmol) triphenylphosphine in 60 mL THF were stirred at room temperature under a nitrogen atmosphere overnight. 3.0 mL water was added and the reaction heated at 70°C for 6 h. The volatiles were evaporated and the remaining water
10 azeotroped with several portions of benzene to give a mixture of crude amine and triphenylphosphine oxide. MS (CI) [M+H]⁺ 448. The crude amine, 0.3 mL (3.17 mmol) acetic anhydride and 0.6 mL (7.42 mmol) pyridine in 75 mL EtOAc were stirred at room temperature under a nitrogen atmosphere overnight. The reaction was extracted with 100 mL water. The organic layer was dried over MgSO₄,
15 filtered and evaporated. Chromatography with 2% MeOH/CH₂Cl₂ afforded (S)-[3-[3-Fluoro-4-(N-(diphenylmethyl)azetidiny-3-oxy)phenyl]-2-oxo-5-oxazolidiny]methylacetamide as a white foam. ¹H NMR (CDCl₃) δ 7.13-7.50 (m, 11H), 6.92-7.03 (m, 1H), 6.70 (t, J=8.9 Hz, 1H), 5.96 (br s, 1H), 4.68-4.85 (m, 2H), 4.45 (s, 1H), 3.97 (t, J=9.0 Hz, 1H), 3.50-3.76 (m, 5H), 3.10-3.19 (m, 2H), 2.03 (s, 3H). MS (CI) [M+H]⁺ 490.
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(S)-N-[3-[3-Fluoro-4-(N-(methanesulfonyl)azetidiny-3-oxy)phenyl]-2-oxo-5-oxazolidiny]methylacetamide (Compound 57):

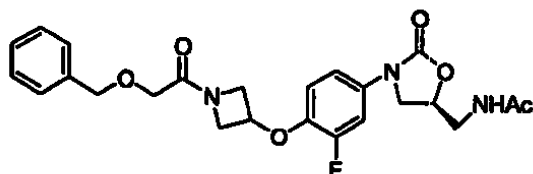
25 To 160 mg (0.327 mmol) (S)-[3-[3-fluoro-4-(N-(diphenylmethyl)azetidiny-3-oxy)phenyl]-2-oxo-5-oxazolidiny]methylacetamide in 5 mL 1,2-dichloroethane, was added 0.04 mL (0.371 mmol) α-chloroethylchloroformate. The reaction was heated at 70°C for 5 h. Ten mL MeOH was added and reflux continued overnight. The volatiles were evaporated to afford the crude hydrochloride salt of the
30 deprotected amine. This was suspended in 20 mL CH₂Cl₂ and 0.15 mL (1.07 mmol) TEA was added followed by 0.1 mL (1.29 mmol) methanesulfonyl chloride. The reaction was stirred overnight, poured into 100 mL water and extracted. The organic layer was washed with 1N HCl (aq), dried over MgSO₄, filtered and

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evaporated. Chromatography with 3% MeOH/CH₂Cl₂ afforded (S)-N-[[3-[3-fluoro-4-{N-(methanesulfonyl)azetidiny]-3-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide as a white foam. ¹H NMR (CDCl₃) δ 7.52 (dd, J=13.1, 2.7 Hz, 1H), 7.06-7.10 (m, 1H), 6.76 (t, J=8.9 Hz, 1H), 5.91 (br t, 1H), 4.87-4.95 (m, 1H), 4.72-4.81 (m, 1H), 4.28 (dd, J=9.7, 6.4 Hz, 2H), 4.09 (dd, J=9.7, 4.8 Hz, 2H), 4.01 (t, J=8.9 Hz, 1H), 3.56-3.77 (m, 3H), 2.93 (s, 3H), 2.02 (s, 3H). MS (CI) [M+H]⁺ 402.

Example 58

(S)-N-[[3-[3-Fluoro-4-{N-(benzyloxyacetyl)azetidiny]-3-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide



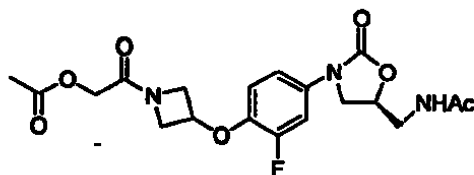
Compound 58

258 mg (0.527 mmol) (S)-[3-[3-fluoro-4-{N-(diphenylmethyl)azetidiny]-3-oxy}phenyl]-2-oxo-5-oxazolidinyl]methylacetamide from Example 57 and 0.20 mL (1.26 mmol) benzyloxyacetyl chloride in 10 mL 1,2-dichloroethane were heated at reflux for 48 h under a nitrogen atmosphere. After cooling, the reaction was diluted with 100 mL CH₂Cl₂ and extracted with 50 mL 1N HCl. The organic layer was washed with water, dried over MgSO₄, filtered and evaporated.

Chromatography with 3% MeOH/CH₂Cl₂ yielded (S)-N-[[3-[3-Fluoro-4-{N-(benzyloxyacetyl)azetidiny]-3-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide as a white powder; mp=119-121°C; MS (CI) [M+H]⁺ 472.

Example 59

(S)-N-[[3-[3-Fluoro-4-{N-(acetoxycetyl)azetidiny]-3-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide



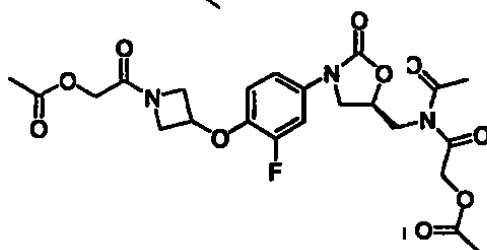
Compound 59

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323 mg (0.660 mmol) (S)-[3-[3-fluoro-4-(N-(diphenylmethyl)azetidiny-3-oxy)phenyl]-2-oxo-5-oxazolidinyl]methylacetamide from Example 57 and 0.2 mL (1.86 mmol) acetoxyacetyl chloride in 15 mL 1,2-dichloroethane were heated at reflux for 24 h. After cooling, the volatiles were evaporated and the residue chromatographed with 3% MeOH/CH₂Cl₂. (S)-N-[[3-[3-Fluoro-4-(N-(acetoxyacetyl)azetidiny-3-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]-acetamide was isolated as a white solid; mp=172-175°C; MS (CI) [M+H]⁺ 424.

Example 60

(S)-N-[[3-[3-Fluoro-4-(N-(acetoxyacetyl)azetidiny-3-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]-N-[α-acetoxyacetyl]acetamide

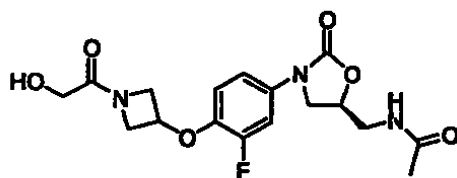


Compound 60

This was also isolated (as a white foam) from the reaction mixture in Example 59. ¹H NMR (CDCl₃) δ 7.53 (dd, J=13.0, 2.8 Hz, 1H), 7.04-7.10 (m, 1H), 6.78 (t, J=8.8 Hz, 1H), 4.95-5.18 (m, 3H), 4.75-4.89 (m, 1H), 4.30-4.68 (m, 5H), 4.00-4.30 (m, 3H), 3.83-3.91 (m, 1H), 3.68-3.79 (m, 1H), 2.47 (s, 3H), 2.02 (s, 3H), 2.18 (s, 3H). MS (CI) [M+Na]⁺ 546.

Example 61

(S)-N-[[3-[3-Fluoro-4-(N-(α-hydroxyacetyl)azetidiny-3-oxy)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide



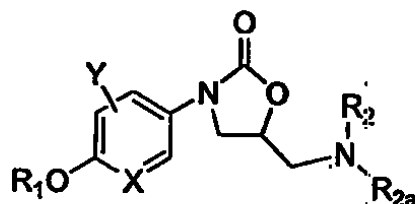
Compound 61

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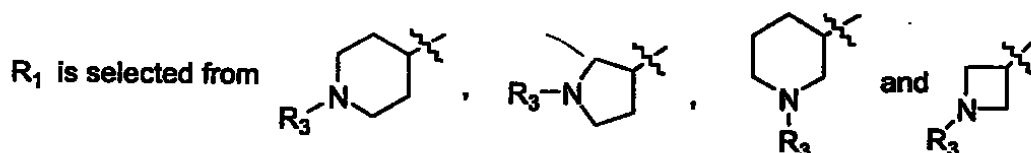
We claim:

1. A compound of Formula I



Formula I

wherein



wherein

(a) R_3 is selected from H, alkyl, $-\text{COR}_4$, $-(\text{CH}_2)_k\text{heteroaryl}$, $-\text{CHR}_5\text{R}_6$, $-(\text{CH}_2)_l\text{aryl}$, $-\text{SO}_2\text{NR}_5\text{R}_6$, and $-\text{SO}_2\text{R}_9$;

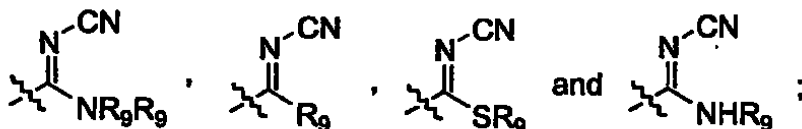
(b) R_4 is selected from H, $-\text{OR}_5$, alkyl, alkylaryl, $-(\text{CH}_2)_m\text{aryl}$, $-(\text{CH}_2)_n\text{heteroaryl}$, $-(\text{CH}_2)_p\text{OR}_5$, $-(\text{CH}_2)_q\text{NR}_7\text{R}_8$, $-\text{CHR}_5\text{R}_6$, and $-\text{NR}_5\text{R}_6$ optionally forming a cyclic amino derivative;

(c) R_5 and R_6 are independently selected from H, alkyl, alkylaryl, haloaryl, $-(\text{CH}_2)_r\text{aryl}$, $-(\text{CH}_2)_s\text{heteroaryl}$, and acyl;

(d) R_7 and R_8 are independently selected from H, alkyl, $-\text{COR}_4$, $-\text{SO}_2\text{R}_9$ and $-\text{CO}_2\text{R}_9$; and

(e) R_9 is selected from H, alkyl, aryl and alkylaryl;

R_2 is selected from $\text{C}(\text{O})\text{R}_9$, $\text{C}(\text{O})\text{OR}_9$,



R_{2a} is H or acyl with the proviso that when R_3 is selected from alkyl, $-(\text{CH}_2)_k\text{aryl}$, $-(\text{CH}_2)_l\text{heteroaryl}$, and $-\text{CHR}_5\text{R}_6$, R_{2a} is H;

X is N or CH;

Y is selected from H, halogen, alkoxy, and alkyl; and

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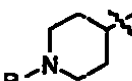
t is an integer of 0 to 4;

or an optical isomer, enantiomer, diastereomer, racemate or racemic mixture thereof, or a pharmaceutically acceptable salt thereof.

2. The compound of Claim 1 wherein X is CH.

3. The compound of Claim 1 wherein R_2 is $-C(O)R_9$ wherein R_9 is as claimed in Claim 1.

4. The compound of Claim 3 wherein R_9 is H or alkyl.

5. The compound of Claim 1 wherein R_1 is  or , wherein R_3 is as claimed in Claim 1.

6. The compound of Claim 5 wherein R_2 is H and R_3 is selected from $-COR_4$, $-SO_2R_5$ and $-(CH_2)_t$ heteroaryl wherein R_4 , R_5 and t are as claimed in Claim 1.

7. The compound of Claim 5 wherein R_4 is selected from $-OR_6$, $-(CH_2)_tOR_6$, alkyl, $-(CH_2)_t$ aryl, and $-(CH_2)_t$ heteroaryl wherein R_6 and t are as claimed in Claim 1.

8. The compound of Claim 7 wherein R_6 is alkyl and R_9 is H or alkyl.

9. A compound of Claim 1 or a pharmaceutically acceptable salt thereof, which is (S)-N-[[3-[3-fluoro-4-{N-(benzyloxyacetyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

10. A compound of Claim 1 or a pharmaceutically acceptable salt thereof, which is (S)-N-[[3-[3-fluoro-4-{N-(α -hydroxyacetyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

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11. A compound of Claim 1 or a pharmaceutically acceptable salt thereof, which is (S)-N-[[3-[3-fluoro-4-{N-(methanesulfonyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

12. A compound of Claim 1 or a pharmaceutically acceptable salt thereof, which is (S)-N-[[3-[3-fluoro-4-{N-(methoxycarbonyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

13. A compound of Claim 1 or a pharmaceutically acceptable salt thereof, which is (S)-N-[[3-[3-fluoro-4-{N-(2-pyrimidinyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

14. A compound of Claim 1 or a pharmaceutically acceptable salt thereof, which is (S)-N-[[3-[3-fluoro-4-{N-(3-cyanobenzoyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

15. A compound of Claim 1 of a pharmaceutically acceptable salt thereof, which is (S)-N-[[3-[3-fluoro-4-{N-(5-cyano-2-pyridyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

16. A compound of Claim 1 or a pharmaceutically acceptable salt thereof, which is (S)-N-[[3-[3-fluoro-4-{N-(2-thienylcarbonyl)piperidinyl-4-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

17. A compound of Claim 1 or a pharmaceutically acceptable salt thereof, which is (S)-N-[[3-[3-fluoro-4-{N-(α -hydroxyacetyl)piperidinyl-3-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

18. A compound of Claim 1 or a pharmaceutically acceptable salt thereof, which is (S)-N-[[3-[3-Fluoro-4-{N-(benzyloxyacetyl)pyrrolidinyl-3-oxy}phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

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19. A pharmaceutical composition comprising a compound of Claim 1 and a pharmaceutically acceptable carrier.

20. A method of treating a subject having a condition caused by or contributed to by bacterial infection, which comprises administering to said subject a therapeutically effective amount of the compound of Formula I as defined in Claim 1.

21. A method of preventing a subject from suffering from a condition caused by or contributed to by bacterial infection, which comprises administering to the subject a prophylactically effective amount of the compound of Formula I as defined in Claim 1.

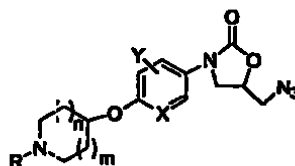
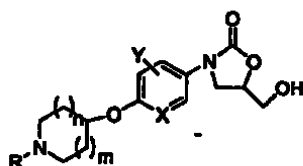
22. The method of Claim 20 or 21 wherein said condition is selected from community-acquired pneumonia, upper and lower respiratory tract infections, skin and soft tissue infections, bone and joint infections, and hospital-acquired lung infections.

23. The method of Claim 20 or 21 wherein said bacterium is selected from *S. aureus*, *S. epidermidis*, *S. pneumoniae*, *Enterococcus* spp., *Moraxella catarrhalis* and *H. influenzae*.

24. The method of Claim 20 or 21 wherein said bacterium is a Gram-positive coccus.

25. The method of Claim 24 wherein said Gram-positive coccus is antibiotic-resistant.

26. An intermediate of Formula e or f



wherein

R is Boc, $-\text{CH}(\text{Ph})_2$ or $-\text{COCH}_2\text{OCH}_2\text{Ph}$;

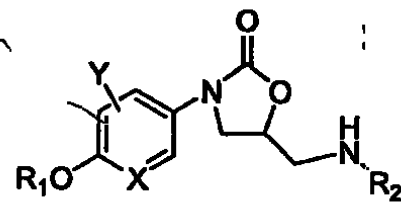
X is N or CH;

5 Y is selected from H, halogen, alkoxy, and alkyl;

n is 0, 1 or 2; and

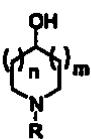
m is 0 or 1.

27. A process for preparing a compound of Formula Ia



Formula Ia

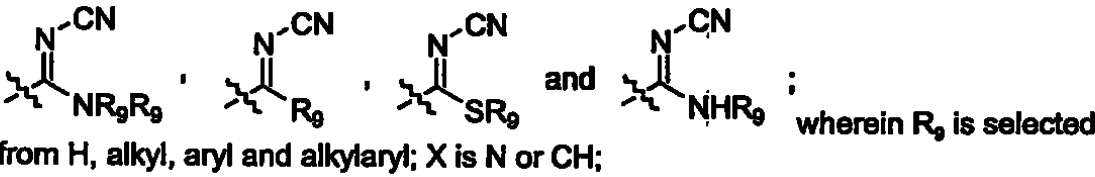
wherein R₁ is a moiety of the formula:



wherein:

R is selected from Boc, $-\text{CH}(\text{Ph})_2$ or $-\text{COCH}_2\text{OCH}_2\text{Ph}$, n is 0, 1 or 2, m is 0 or 1,

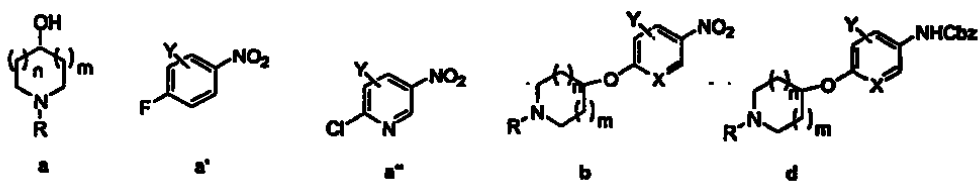
15 R₂ is selected from $\text{C}(\text{O})\text{R}_9$, $\text{C}(\text{O})\text{OR}_9$,



Y is selected from H, halogen, alkoxy, and alkyl;

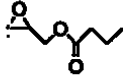
20 which process comprises:

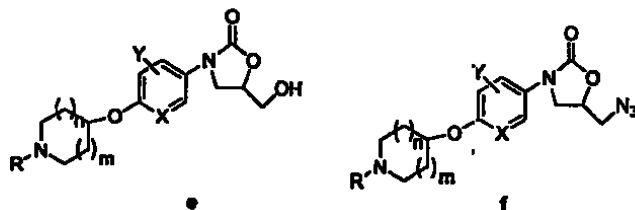
(a) reacting a compound of Formula a with a compound of Formula a' or a'' to form a compound of Formula b;



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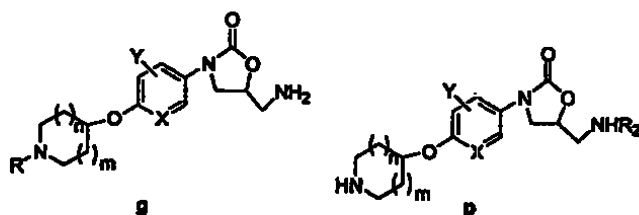
(b) converting the compound of Formula b to a compound of Formula d;

(c) reacting the compound of Formula d with  to form a compound of Formula e;



(d) converting the compound of Formula e to a compound of Formula f;

(e) converting the compound of Formula f to a compound of Formula g;



(f) converting the compound of Formula g to a compound of Formula p; and

(g) converting the compound of Formula p to a compound of Formula la.

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DECLARATION AND POWER OF ATTORNEY FOR PATENT APPLICATION

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled PIPERIDINYLOXY AND PYRROLIDINYLOXY OXAZOLIDINONE ANTIBACTERIALS, the specification of which

(check one) ☒ is attached hereto.

☐ was filed on _____ as

Application Serial No. _____

and was amended on _____
(if applicable)

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, §119 (a)-(d) or §365(b) of any foreign application(s) for patent or inventor's certificate, or §365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed.

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Prior Foreign Application(s):

Country	Application Number	Date of Filing	Priority Claimed Under 35 U.S.C. 119	
			☐ YES	☐ NO
			☐ YES	☐ NO
			☐ YES	☐ NO

I hereby claim the benefit under Title 35, United States Code, §119(e) of any United States provisional application(s) listed below:

60/172,923
(Application Number)

December 21, 1999
(Filing Date)

(Application Number)

(Filing Date)

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

<u>Application Serial No.</u>	<u>Filing Date</u>	<u>Status</u>
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<u>Application Serial No.</u>	<u>Filing Date</u>	<u>Status</u>
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I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith as well as to file equivalent patent applications in countries foreign to the United States including the filing of international patent applications in accordance with the Patent Cooperation Treaty: Steven P. Berman (Reg. #24,772), Andrea L. Colby (Reg. #30,194), Paul A. Coletti (Reg. #32,019), Matthew S. Goodwin (Reg. #32,839), Ralph R. Palo (Reg. #29,486), Bernard F. Plantz (Reg.

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#32,091), Joseph F. Shirtz (Reg. #31,880), Michael Stark (Reg. #32,495), Mark R. Warfield (Reg. #33,463), and Kenneth J. Dow (Reg. #32,890) One Johnson & Johnson Plaza, New Brunswick, NJ 08933.

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Address all correspondence to Philip S. Johnson, One Johnson & Johnson Plaza, New Brunswick, NJ 08933-7003.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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Inventor, If Any

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Inventor, If Any

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