Title: A NOVEL OXAZOLIDINONE DERIVATIVE AND MANUFACTURING PROCESS THEREOF

Abstract: The present invention relates to novel oxazolidinone compound represented by general formula I or a their pharmaceutically acceptable salts and a process for the preparation thereof. The compounds of the present invention have wide antibacterial spectrum, superior antibacterial activity. Therefore, the compound of the present invention can be used as an antibacterial agent.
Description

A NOVEL OXAZOLIDINONE DERIVATIVE AND MANUFACTURING PROCESS THEREOF

Technical Field

[1] The present invention relates to triacyl methyl oxazolidinone derivatives of formula I with antibacterial activity, their pharmaceutically acceptable salts, pharmaceutical compositions comprising the same, a preparation method thereof.

[2]


[4]

[5] wherein R is hydrogen atom, ethylcarboxylate, amide, diethoxymethyl, aldehyde, hydroxoyxime or nitrile;

[6] X is each and independently carbon or nitrogen atom; and

[7]

---

is single bond or double bond.

[8]

Background Art

[9] The oxazolidinones developed in 1980s represent a new class of antibacterial agents which showed activity of wide spectrum against gram-positive bacterial infections, including those infections caused by strains resistant to other antibiotics. The oxazolidinones are a relatively new class of orally active, totally synthetic antibacterial agents which have no cross-resistance with other antibiotics.

[10]


[12] Formula A

[13]
Subsequently, Pharmacia and Upjohn Co. reported two kinds of potent oxazolidinone antibacterial agents, linezolid (formula B) and eperezolid (formula C). These compounds showed good activity against gram-positive bacterial infections, including the resistant strain of methicillin-resistant Staphylococcus aureus (MRSA), penicillin-resistant Streptococcus pneumoniae (PRSP) and vancomycin-resistant enterococci (VRE). The compounds showed similar antimicrobial activity to vancomycin. However, oxazolidinones generally show a very low activity against aerobic gram-negative organism.

Thus, the present inventors carried out an intensive study for new derivatives of oxazolidinone antibacterial agents and at last found out the fact that the oxazolidinone derivatives of the general formula I have strong antimicrobial activity.

The oxazolidinone derivatives of the general formula I were not reported, have antimicrobial activities of wide spectrum and have excellent antimicrobial activities in vivo.
Disclosure of Invention

Technical Problem

Therefore, one object of the present invention is to provide oxazolidinone derivatives of formula I and pharmaceutically acceptable salt thereof which can be used as an antibiotic exhibiting higher activities against multi-drug resistant strains (MRSA).

The other object of the present invention is to provide a process for preparing such an oxazolidinone derivatives of formula I or its pharmaceutically acceptable salt.

Technical Solution

There are provided oxazolidinone derivatives represented by the following general formula I and pharmaceutically acceptable salt thereof.

Formula I

\[
\begin{align*}
\text{X} &\quad \text{X} \\
\text{R} &\quad \text{F} \\
\text{N} &\quad \text{N} \\
\text{O} &\quad \text{O} \\
\text{N} &\quad \text{N}
\end{align*}
\]

wherein R is hydrogen atom, ethylcarboxylate, amide, diethoxymethyl, aldehyde, hydroxoyxime or nitrile;

X is each and independently carbon or nitrogen atom; and

---

is single bond or double bond.

Among the oxazolidinone derivatives of the general formula I, representative compounds are shown below.

Formula I-1

\[
\begin{align*}
\text{N} &\quad \text{N} \\
\text{F} &\quad \text{O} \\
\text{N} &\quad \text{N}
\end{align*}
\]
[42] Formula I-2

[43]

[44]

[45] Formula I-3

[46]

[47]

[48] Formula I-4

[49]

[50]

[51] Formula I-5

[52]

[53]

[54] Formula I-6

[55]

[56]

[57] Formula I-7

[58]

[59]
[60]  
Formula I-8

[61]

[62]  
Formula I-9

[63]

[64]

[65]  
Formula I-10

[66]

[67]

[68]

[69]  
Formula I-11

[70]

[71]  
Formula I-12

[72]

[73]

[74]  
Formula I-13

[75]

[76]
Hereinafter, a preparation method of the compound represented by the general I will be described by the following schemes 1–3.

Scheme 1

wherein R is the same defined in the general formula I.

The general preparation involved nucleophilic aromatic substitution reaction between the pyrrolidine or pyrrole and 3,4-difluoronitrobenzene (1-1) to give the 3-fluoro-4-azolylNitrobenzene intermediates. Reduction of the nitro group by hydrogenation in the presence of palladium on carbon catalyst and Cbz protection of the resulting aniline gave intermediates (1-2). Deprotonation with base (n-BuLi) followed by treatment with (R)-(−)-glycidyl butyrate afforded oxazolidinones (1-3). The hydroxymethyl side chain was then elaborated to the azide analogue (1-4') via standard transformations. Formation of the azide followed by 1,3-dipolar cycloaddition in refluxing vinyl acetate gave triazolylmethyl oxazolidinone (Formula I-1).

4-Substituted pyrrole were synthesized in using similar method and also, 4-pyrazole
analogue were synthesized utilizing the ethyl 4-pyrazolecarboxylate analogue. This material was prepared in a regioselective manner. The arylhydrazone was synthesized and condensed with the known (ethoxycarbonyl)malondialdehyde to give the ethyl 4-pyrazolecarboxylate.

[90] Scheme2

[92] wherein R is the same defined in the general formula I.

[94] And also, treatment of an acetonitrile solution of 3,4-difluoronitrobenzene (1-1) with benzylamine in the presence of triethylamine afforded in high yield. The nitro group of structure is then reduced by hydrogenation in the presence of platinum catalyst in a suitable solvent such as THF or Methanol is to give compound (2-1). The aniline (2-1) is then converted to its Cbz intermediate and then deprotonated by n-BuLi in THF to give a lithiated intermediate which is then treated with commercially available (R)-(-)-glycidyl butyrate. Warming to ambient temperature affords the compound (2-2). This alcohol (2-2) is then converted to the corresponding mesylate. The resultant sulfonate derivative is then reacted with sodium azide in DMF to provide the azide (2-3) analogue, which is then cyclized by refluxing vinyl acetate. And then triazole was deprotected by hydrogenation to afford key intermediate aniline (2-4). The aniline (2-4) was condensed with 2,5-dimethoxy-3-tetrahydrofurancarboxaldehyde to yield the formylpyrrole (formula I-3) which was exploited for the preparation of oximepyrrole (formula I-4) via standard transformations. Dehydration of the oxime with trichloroacetyl chloride in dichloromethane yielded the 3-cyano analogue (formula I-5).

[96] Scheme3

[98]
wherein R is the same defined in the general formula I.

The amine (2-4) is then reacted with sodium nitrite, sodium azide and sodium acetate in hydrochloride to provide the azide analogue (3-1) which is then cyclized by refluxing vinyl acetate or propiolaldehyde diethylacetal to afforded triazolylmethyl oxazolidinones (formula I-6 or formula I-8). Deprotection of the diethylacetal with trifluoroacetic acid afforded the 4-carbaldehydetriazole (formula I-8), which was exploited for the preparation of 4-oximepyrrole (formula I-9) via standard transformations. Dehydration of the oxime (formula I-10) with trichloroacetyl chloride in dichloromethane yielded the 4-cyano analogue (formula I-11). And also reaction of the amine (2-4) with triethyl orthoformate and sodium azide afforded the tetrazole oxazolidinone (formula I-7).

The compound of formula I-1~14 may be used in its native form or as pharmaceutically acceptable salt. In cases where forming a stable nontoxic acid or base salt is desired, administration of the compound as a pharmaceutically acceptable salt may be appropriate. Pharmaceutically acceptable salts may be obtained using standard procedures well known in the art, alkali metal (for example, sodium or potassium) or alkaline earth metal (for example, calcium or magnesium) salts of carboxylic acids can be made. And reacting a sufficiently basic compound such as an amine with a suitable acid affording a physiologically acceptable anion (for example, ammonium, triethylamine, pyridine and N,N-dimethylethanolamine salt). Suitable inorganic salts are formed, including hydrochloride, hydrobromide, sulfate and nitrate salts. Organic acid addition salts may also be formed with acids which form a physiological acceptable anion, for example, formic acid, acetic acid, tartaric acid, citric acid, methylsulfonic acid, lactic acid, succinic acid and benzenesulfonic acid.

**Advantageous Effects**

It is found that not only does the compound of formula I-1~14 show inhibitory
activity against a broad spectrum of bacteria, but its antibacterial activity is excellent in vivo. For example, the compound of the present invention can exert potent antibacterial activity versus various human and animal pathogens, including gram-positive bacteria such as Staphylococi, Enterococci and Streptococci, anaerobic microorganism, such as Bacteroides and Clostridia, and acid-resistant microorganism such as Mycobacterium tuberculosis and Mycobacterium avium.

Best Mode for Carrying Out the Invention

Experimental example 1

MIC Test Method

The in vitro Minimum Inhibitory Concentration (MIC: µg/ml) of test compounds were determined by a standard agar dilution method. (Chemotheraphy, 1981, 29 (1), 76). Linezolid is included in the assay and serves as a comparator and quality control compound of test compounds. The activity of compounds of this invention is shown in Table 1 and Table 2.

Table 1

<table>
<thead>
<tr>
<th>organism</th>
<th>compound</th>
<th>(MIC) (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>L2D</td>
</tr>
<tr>
<td>Str. pyogenes T7A</td>
<td>0.8</td>
<td>0.4</td>
</tr>
<tr>
<td>Str. faecium MD 8b</td>
<td>1.6</td>
<td>1.6</td>
</tr>
<tr>
<td>S. aureus SG 511</td>
<td>1.6</td>
<td>1.6</td>
</tr>
<tr>
<td>S. aureus 285</td>
<td>1.6</td>
<td>0.8</td>
</tr>
<tr>
<td>S. aureus 503</td>
<td>1.6</td>
<td>1.6</td>
</tr>
<tr>
<td>MRSA 2</td>
<td>1.6</td>
<td>1.6</td>
</tr>
<tr>
<td>MRSA 6</td>
<td>1.6</td>
<td>1.6</td>
</tr>
<tr>
<td>MRSA 30</td>
<td>1.6</td>
<td>0.8</td>
</tr>
<tr>
<td>MRSA 32</td>
<td>1.6</td>
<td>0.8</td>
</tr>
<tr>
<td>MRSA 35</td>
<td>1.6</td>
<td>0.8</td>
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Table 2
<table>
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<tr>
<th>organism</th>
<th>LZD</th>
<th>I-9</th>
<th>I-10</th>
<th>I-11</th>
<th>I-12</th>
<th>I-14</th>
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<td>S. aureus Met R</td>
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<td>6.3</td>
<td>3.1</td>
<td>1.6</td>
</tr>
<tr>
<td>S. aureus Met S</td>
<td>1.6</td>
<td>0.8</td>
<td>1.6</td>
<td>3.1</td>
<td>1.6</td>
<td>0.8</td>
</tr>
<tr>
<td>Coagulase negative S. Met R</td>
<td>6.3</td>
<td>0.4</td>
<td>1.6</td>
<td>0.8</td>
<td>1.6</td>
<td>0.4</td>
</tr>
<tr>
<td>Coagulase negative S. Met S</td>
<td>1.6</td>
<td>0.4</td>
<td>1.6</td>
<td>0.8</td>
<td>1.6</td>
<td>1.6</td>
</tr>
<tr>
<td>Enterococcus faecalis Van R</td>
<td>6.3</td>
<td>1.6</td>
<td>1.6</td>
<td>6.3</td>
<td>3.1</td>
<td>0.4</td>
</tr>
<tr>
<td>Enterococcus faecalis Van S</td>
<td>1.6</td>
<td>1.6</td>
<td>1.6</td>
<td>3.1</td>
<td>1.6</td>
<td>0.4</td>
</tr>
<tr>
<td>Enterococcus faecium Van R</td>
<td>6.3</td>
<td>0.8</td>
<td>1.6</td>
<td>0.8</td>
<td>3.1</td>
<td>0.8</td>
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<td>Enterococcus faecium Van S</td>
<td>6.3</td>
<td>0.4</td>
<td>1.6</td>
<td>3.1</td>
<td>0.4</td>
<td>0.2</td>
</tr>
<tr>
<td>Str. pneumoniae Pen NS</td>
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<td>0.2</td>
<td>0.2</td>
<td>0.8</td>
<td>0.8</td>
<td>0.2</td>
</tr>
<tr>
<td>Str. pneumoniae Pen S</td>
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<td>0.2</td>
<td>0.4</td>
<td>0.8</td>
<td>3.1</td>
<td>0.8</td>
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<tr>
<td>Str. Pyogenes</td>
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<td>0.2</td>
<td>0.8</td>
<td>0.4</td>
<td>0.8</td>
</tr>
<tr>
<td>Str. Agalactiae</td>
<td>3.1</td>
<td>0.4</td>
<td>0.4</td>
<td>0.8</td>
<td>0.8</td>
<td>0.4</td>
</tr>
<tr>
<td>H. influenzae Beta +</td>
<td>6.3</td>
<td>1.6</td>
<td>1.6</td>
<td>6.3</td>
<td>0.8</td>
<td>1.6</td>
</tr>
</tbody>
</table>

LZD: Linezolid

[115] As can be seen from Tables 1 and 2, the oxazolidinone antibacterial agents of the present invention have excellent activity against gram-positive bacterial infection, including MRSA strains.

[116] Experimental example 2

Acute toxicity studies

[117] In order to illustrate usefulness of the compounds of the present invention, acute toxicity test of the compounds synthesized in the Examples were carried out. Each dose of the compounds dissolved in 50% PEG (Polyethylene glycol) was determined in mice using oral route of administration. Mortalities of the animals were recorded 2 weeks later, the results of the acute toxicity studies are shown in Table 3.

[120] Table 3
<table>
<thead>
<tr>
<th>compound</th>
<th>LD$_{50}$ (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>compound I-1</td>
<td>&gt;5000</td>
</tr>
<tr>
<td>compound I-3</td>
<td>&gt;5000</td>
</tr>
<tr>
<td>compound I-4</td>
<td>&gt;4000</td>
</tr>
<tr>
<td>compound I-5</td>
<td>&gt;4000</td>
</tr>
<tr>
<td>compound I-9</td>
<td>&gt;5000</td>
</tr>
<tr>
<td>compound I-10</td>
<td>&gt;5000</td>
</tr>
<tr>
<td>compound I-14</td>
<td>&gt;5000</td>
</tr>
</tbody>
</table>

* Mouse: Male ICR strain, 4 weeks

[124] The compounds are shown high stability as an antimicrobial medicament from LD$_{50}$ >4000mg/kg in oral routes. Accordingly, the compounds of the present invention can be used in the therapeutic treatment of human beings or animals infected with variety of gram-positive bacteria.

[126] The present invention includes within its scope pharmaceutical compositions comprising one or more of the compound I-1 and their derivatives as active ingredients, in association with pharmaceutically acceptable carriers, excipients or other additives, if necessary. The compositions may be formulated into various forms such as tablets, capsules, troche, suspension, solution, suppositories, ointment, cream, injection, which may contain conventional additives such as a dispersant, suspending agent, stabilizer and the like. The compounds of formula I according to this invention are administered orally and parenterally, i.e., by injection, for example, by intravenous injection or by other parenteral routes of administration. Pharmaceutical compositions for parenteral administration will generally contain a pharmaceutically acceptable amount of the compound according to formula I as a soluble salt (acid addition salt or base salt) dissolved in a pharmaceutically acceptable liquid carrier such as, for example, water-for-injection and a buffer to provide a suitably buffered isotonic solution. Suitable buffering agents include, for example, L-(+)-lysine, L-(+)-arginine, N-methylglucamine, sodium citrate, sodium bicarbonate and trisodium orthophosphate to name but a few representative buffering agents.

[128] Formulation examples are described below.
Formulation example 1

Excipient Amount
The compound of prepared Example 1 400.0mg
Corn starch 40.0mg
Microcrystalline cellulose (intragranular) 16.0mg
hydroxypropylcellulose (binder solution) 2.08mg
Microcrystalline cellulose (extragranular) 70.0mg
Crocarmellose sodium 30.0mg
Magnesium stearate 5.6mg
Water purified

Film coating phase
Opadry white YS-1-18202-A 16.8mg
Water purified 129.2mg

Polisher
Carnauba wax 0.0224mg

The following preparative examples are provided to further illustrate this invention but they do not limit the scope of the present invention.

Example 1
3-(3-Fluoro-4-pyrrolidin-1-yl-phenyl)-5-[1,2,3]triazol-1-ylmethyl-oxazolidin-2-one (I-1):

\[ \text{Vinylacetate 3.5ml and 5-azidomethyl-3-(3-fluoro-4-pyrrolidin-1-yl-phenyl)-oxazolidin-2-one (50mg, 0.16mmol) [Chem. Pharm. Bull. 2001, 49, 353-360] were heated to 110°C for 30h, followed by cooling and concentration in vacuo. The residue was purified by silica gel column chromatography (ethylacetate/hexane = 10/1) to afford the title compound (40mg) in a yield of 74%.} \]
[156] $^1$H NMR (CDCl$_3$) $\delta$ ppm: 7.78 (2H, dd), 7.27 (1H, dd), 6.88 (1H, dd), 6.58 (1H, dd), 5.01 (1H, m), 4.77 (2H, dd), 4.10 (1H, dd), 3.83 (1H, dd), 3.33 (4H, dd), 2.01 (4H, dd)

[157]

[158] **Example 2**

[159] 3-(3-Fluoro-4-pyrrol-1-yl-phenyl)-5-[1,2,3]triazol-1-ylmethyl-oxazolidin-2-one (I-2):

[160]

Vinylacetate 12.5ml and 5-azidomethyl-3-(3-fluoro-4-pyrrol-1-yl-phenyl)-oxazolidin-2-one (176mg, 0.585mmol) [J. Med. Chem. 2000, 43, 953-970] were heated to 110°C for 30h, followed by cooling and concentration in vacuo. The residue was purified by silica gel column chromatography (ethylacetate/hexane = 10/1) to afford the title compound (148mg) in a yield of 77%.

[161] $^1$H NMR (DMSO-d$_6$) $\delta$ ppm: 8.18 (1H, dd), 7.76 (1H, dd), 7.56 (2H, dd), 7.36 (1H, dd), 7.10 (2H, dd), 6.25 (2H, dd), 5.17 (1H, m), 4.85 (2H, dd), 4.27 (1H, dd), 3.92 (1H, dd)

[162]

[163] **Example 3**

[164] Benzyl-[2-fluoro-4-(2-oxo-5-[1,2,3]triazol-1-ylmethyl-oxazolidin-3-yl)-phenyl]-carbamic acid benzyl ester

[165]

Vinylacetate 8.3ml and [4-(5-azidomethyl-2-oxo-oxazolidin-3-yl)-2-fluoro-phenyl]-benzyl-carbamic acid benzyl ester (185mg, 0.39mmol) were heated to 110°C for 30h, followed by cooling and concentration in vacuo. The residue was purified by silica gel column chromatography (ethylacetate/hexane = 3/1) to afford the title compound (150mg) in a yield of 77%.

[166] $^1$H NMR (CDCl$_3$) $\delta$ ppm: 7.45-6.50 (13H, m), 4.95 (1H, m), 4.92 (2H, dd), 4.73
(2H, dd), 4.67 (2H, dd), 4.28 (2H, dd), 4.01 (1H, dd), 3.78 (1H, dd)

[169]

Example 4

[171] 3-(4-Amino-3-fluoro-phenyl)-5-[1,2,3]triazol-1-ylmethyl-oxazolidin-2-one:

![Chemical Structure]

[173] A solution of benzyl-[2-fluoro-4-(2-oxo-5-[1,2,3] triazol-1-ylmethyl-oxazolidin-3-yl)-phenyl]-carbamic acid benzyl ester (150mg, 0.3mmol) in ethanol (9.3ml) was added 62mg of 10% Pd/C catalyst. The mixture was placed on a Parr hydrogenator for 7.5h. There was then added an additional 6.1mg of 10% Pd/C catalyst and the reaction was allowed to continue. After an additional 15.5h the catalyst was removed by filtration through Celite and the filtrate was concentrated in vacuo to afford the title compound (69mg) in a yield of 83%.

[174] $^1$H NMR (CD OD) δ ppm: 8.02 (1H, s), 7.73 (1H, s), 7.15 (1H, dd), 6.80 (2H, dd), 5.09 (1H, m), 4.82 (2H, dd), 4.18 (1H, dd), 3.87 (1H, dd)

[176] Example 5

[177] 1-[2-Fluoro-4-(2-oxo-5-[1,2,3]triazol-1-ylmethyl-oxazolidin-3-yl)-phenyl]-1H-pyrrole-3-carbaldehyde (I-3):

![Chemical Structure]

[179] A solution of 3-(4-amino-3-fluoro-phenyl)-5-[1,2,3] triazol-1-ylmethyl-oxazolidin-2-one (48mg, 0.17mmol) and 2,5-dimethoxy-3-tetrahydrofurancarboxaldehyde (34μl, 0.24mmol) in acetic acid (1.2ml) was refluxed for 2h. The solution was cooled and the solvent removed under high vacuum, azeotroping the residue with toluene to remove the last traces of acetic acid. The residue was chromatographed (ethylacetate/hexane/methanol = 4/4/1) to afford the title compound (45mg) in a yield of 73%.

[180] $^1$H NMR (CD OD) δ ppm: 9.85 (1H, s), 7.79-6.80 (8H, dd), 5.12 (1H, m), 4.83 (2H, dd), 4.18 (2H, dd)
Example 6

1-[2-Fluro-4-(2-oxo-5-[1,2,3]triazol-1-ylmethyl-oxazolidin-3-yl)-phenyl]-1H-pyrrole-3-carbaldehyde oxime (I-4):

\[
\begin{align*}
&N & & F \\
&\text{H} & & O \\
&\text{N} & & N
\end{align*}
\]

1-[2-Fluro-4-(2-oxo-5-[1,2,3]triazol-1-ylmethyl-oxazolidin-3-yl)-phenyl]-1H-pyrrole-3-carbaldehyde (74mg, 0.21mmol), hydroxylamine hydrochloride (10mg, 0.15mmol) and potassium carbonate (15mg, 0.11mmol) were stirred in methanol/dichloromethane (1:1) (0.5ml/0.5ml) for overnight. And then the resulting precipitate was collected, washed with water and dried under vacuum to yield 48mg (63%) of title compound.

\[\text{^1H NMR (DMSO-d}_6\text{) } \delta \text{ ppm: 10.58 (1H, s), 8.17-6.47 (8H, dd), 5.17 (1H, m), 4.84 (2H, dd), 4.27 (1H, dd), 3.95 (1H, dd)}\]

Example 7

1-[2-Fluro-4-(2-oxo-5-[1,2,3]triazol-1-ylmethyl-oxazolidin-3-yl)-phenyl]-1H-pyrrole-3-carbonitrile (I-5):

To a stirred solution of the 1-[2-fluro-4-(2-oxo-5-[1,2,3] triazol-1-ylmethyl-oxazolidin-3-yl)-phenyl]-1H-pyrrole-3-carbaldehyde oxime (78mg, 0.22mmol) and triethylamine (60\(\mu\)l, 0.43mmol) in dichloromethane (1ml), a solution of trichloroacetyl chloride (24.7\(\mu\)l, 0.22mmol) in dichloromethane (1ml) is added dropwise at 5-10°C. The mixture is allowed to reach room temperature and is stirred for 24h. The mixture was diluted with dichloromethane and washed with water. Drying (magnesium sulfate) and concentration in vacuo, the residue was purified by silica gel column chromatography (dichloromethane/methanol = 9/1) to afford the title compound (34mg) in a yield of 45%.

\[\text{^1H NMR (DMSO-d}_6\text{) } \delta \text{ ppm: 7.97-6.60 (8H, dd), 5.18 (1H, m), 4.88 (2H, dd), 4.29}\]
(1H, dd), 4.01 (1H, dd)

Example 8

3-(4-Azido-3-fluoro-phenyl)-5-[1,2,3]triazol-1-ylmethyl-oxazolidin-2-one:

3-(4-Amino-3-fluoro-phenyl)-5-[1,2,3]triazol-1-ylmethyl-oxazolidin-2-one (61mg, 0.22mmol) was dissolved in concentrated hydrochloride 0.5ml and water 0.5ml and cooled to 0°C. Sodium nitrite (17mg, 0.24mmol) was added and the yellow solution was stirred at 0°C for 2h. A solution of sodium azide (29mg, 0.44mmol) and sodium acetate (360mg, 4.39mmol) was added dropwise. The mixture was extracted with ethyl acetate and the combined extracts were washed with brine and dried (magnesium sulfate). Removal of solvent gave product as a tan solid. This was crystallized from ethyl acetate/hexane to give 45mg in a yield of 67%.

1H NMR (DMSO-d6) δ ppm: 8.15 (1H, s), 7.75 (1H, s), 7.54 (1H, dd), 7.30 (2H, dd), 5.13 (1H, m), 4.82 (2H, dd), 4.21 (1H, dd), 3.87 (1H, dd)

Example 9

3-(3-Fluoro-4-[1,2,3]triazol-1-yl-phenyl)-5-[1,2,3]triazol-1-ylmethyl-oxazolidin-2-one (I-6):

Vinylacetate 2.6ml and 3-(4-azido-3-fluoro-phenyl)-5-[1,2,3] triazol-1-ylmethyl-oxazolidin-2-one (36mg, 0.12mmol) were heated to 110°C for 30h, followed by cooling and concentration in vacuo. The residue was purified by silica gel column chromatography (ethyl acetate/hexane/methanol = 4/4/1) to afford the title compound (40mg) in a yield of 99%.

1H NMR (CDCl3) δ ppm: 8.22 (1H, s), 8.00 (1H, s), 7.86 (2H, dd), 7.75 (2H, dd), 7.35 (1H, dd), 5.20 (1H, m), 4.92 (2H, dd), 4.33 (1H, dd), 4.06 (1H, dd)
Example 10

3-(3-Fluoro-4-tetrazol-2-yl-phenyl)-5-[1,2,3]triazol-1-ylmethyl-oxazolidin-2-one (I-7):

A slurry of 3-(4-amino-3-fluoro-phenyl)-5-[1,2,3]triazol-1-ylmethyl-oxazolidin-2-one (36mg, 0.13mmol), sodium azide (13mg, 0.19mmol) and triethyl orthoformate (34μl, 0.2mmol) in acetic acid (0.68ml) was refluxed for 4h. The mixture was cooled and added to ice water (1.4ml). After setting at ambient temperature for 48h, the precipitated product was collected by filtration and washed with cold methanol to yield 27mg (63%).

\(^1\)H NMR (DMSO-d_6) δ ppm: 9.91 (1H, s), 8.17 (1H, dd), 7.91-7.50 (4H, m), 5.19 (1H, m), 4.85 (2H, dd), 4.31 (1H, dd), 3.98 (1H, dd)

Example 11

3-(3-Fluoro-4-pyrrolidin-1-yl-phenyl)-5-[1,2,3]triazol-1-ylmethyl-oxazolidin-2-one hydrochloride:

 Etheral hydrochloride (3ml) was added dropwise to a solution of I-1 (32mg, 0.10mmol) in chloroform (1ml) and was concentrated in vacuo. The residue was treated with water (3ml) and the suspended solid was removed by filtration and washed with additional water. The combined filtrates were freeze-dried to yield 28mg (79%).

Example 12

3-(3-Fluoro-4-pyrrol-1-yl-phenyl)-5-[1,2,3]triazol-1-ylmethyl-oxazolidin-2-one hydrochloride:

 Etheral hydrochloride (3ml) was added dropwise to a solution of I-2 (30mg, 0.09mmol) in chloroform (1ml) and was concentrated in vacuo. The residue was treated with water (3ml) and the suspended solid was removed by filtration and washed with additional water. The combined filtrates were freeze-dried to yield 31mg (94%).

Example 13
1-[2-Fluoro-4-(2-oxo-5-[1,2,3]triazol-1-ylmethyl-oxazolidin-3-yl)-phenyl]-1H-pyrrole-3-carbonitrile hydrochloride:

Etheral hydrochloride (3ml) was added dropwise to a solution of I-5 (32mg, 0.09mmol) in chloroform (1ml) and was concentrated in vacuo. The residue was treated with water (3ml) and the suspended solid was removed by filtration and washed with additional water. The combined filtrates were freeze-dried to yield 30mg (86%).

Example 14

3-3-Fluoro-4-pyrrolidin-1-yl-phenyl)-5-[1,2,3]triazol-1-ylmethyl-oxazolidin-2-one sulfuric acid:

Sulfuric acid (1ml) was added to a solution of I-1 (30mg, 0.09mmol) in isopropylalcohol (1ml) and was concentrated in vacuo afforded a solid which was recrystallized from boiling isopropylalcohol to afford title compound 32mg (82%)

Example 15

3-3-Fluoro-4-pyrrol-1-yl-phenyl)-5-[1,2,3]triazol-1-ylmethyl-oxazolidin-2-one sulfuric acid:

Sulfuric acid (1ml) was added to a solution of I-2 (32mg, 0.1mmol) in isopropylalcohol (1ml) and was concentrated in vacuo afforded a solid which was recrystallized from boiling isopropylalcohol to afford title compound 36mg (87%)

Example 16

1-[2-Fluoro-4-(2-oxo-5-[1,2,3]triazol-1-ylmethyl-oxazolidin-3-yl)-phenyl]-1H-pyrrole-3-carbonitrile sulfuric acid:

Sulfuric acid (1ml) was added to a solution of I-5 (31mg, 0.09mmol) in isopropylalcohol (1ml) and was concentrated in vacuo afforded a solid which was recrystallized from boiling isopropylalcohol to afford title compound 31mg (79%)

Example 17

3-3-Fluoro-4-pyrrolidin-1-yl-phenyl)-5-[1,2,3]triazol-1-ylmethyl-oxazolidin-2-one citric acid:

Citric acid (1eq) was added to a solution of I-1 (30mg, 0.09mmol) in isopropylalcohol (1ml) and was concentrated in vacuo afford a solid which was recrystallized from boiling isopropylalcohol to afford title compound 31mg (65%).
Example 18
3-(3-Fluoro-4-pyrrol-1-yl-phenyl)-5-[1,2,3]triazol-1-ylmethyl-oxazolidin-2-one citric acid:
Citric acid (1eq) was added to a solution of I-2 (30mg, 0.09mmol) in isopropylalcohol (1ml) and was concentrated in vacuo afford a solid which was recrystallized from boiling isopropylalcohol to afford title compound 29mg (62%).

Example 19
1-[2-Fluoro-4-(2-oxo-5-[1,2,3]triazol-1-ylmethyl-oxazolidin-3-yl)-phenyl]-1H-pyrrole-3-carbonitrile citric acid:
Citric acid (1eq) was added to a solution of I-5 (30mg, 0.08mmol) in isopropylalcohol (1ml) and was concentrated in vacuo afford a solid which was recrystallized from boiling isopropylalcohol to afford title compound 29mg (62%).

Example 20
(R)-5-((1H-1,2,3-triazol-1-yl)methyl)-3-(4-(4(diethoxymethyl)-1H-1,2,3-triazol-1-yl)-3-fluorophenyl)oxazolidin-2-one(I-8)

\[
\begin{align*}
\text{\text{O}} \\
\text{F} \\
\end{align*}
\]

A solution of propiolardehyde diethylacetal 333\mu l and 3-(4-azido-3-fluoro-phenyl)-5-[1,2,3]triazol-1-ylmethyl-oxazolidin-2-one (320mg, 1.15mmol) in benzene (3ml) were refluxed for 30h. The residue was purified by silica gel column chromatography (ethyl acetate/hexane/methanol = 4/4/1) to afford the title compound (266mg) in a yield of 58%.

\(^1\)H NMR (CDCl\(_3\)) \(\delta\) ppm: 8.08 (1H, dd), 7.90 (1H, dd), 7.82 (1H, dd), 7.76 (1H, dd), 7.63 (1H, dd), 7.21 (1H, dd), 5.80 (2H, dd), 5.15 (1H, m), 4.84 (2H, dd), 4.25 (1H, dd), 4.10 (1H, dd), 3.70 (4H, dd), 1.28 (6H, dd)

Example 21
1-((4-((R)-5-((1H-1,2,3-triazol-1-yl)methyl)-2-oxooxazolidin-3-yl)-2-fluorophenyl)-1H-1,2,3-triazole-4-carbaldehyde(I-9)

[239] [240] [241] [242] [243] [244] [245] [246] [247] [248] [249] [250] [251] [252] [253] [254] [255] [256]
[257] 3-[4-(4-Diethoxymethyl-[1,2,3]triazol-1-yl)-3-fluoro-phenyl]-5-[1,2,3]triazol-1-ylmethyl-oxazolidin-2-one (75mg, 0.17mmol) was dissolved in chloroform 1.0ml and cooled to 0°C. 50% aqueous trifluoroacetic acid (350μl, 4.5mmol) was added and the solution was stirred at 0°C for 90min. The mixture was extracted with methylene chloride, water and aq.NaHCO₃. Drying (magnesium sulfate) and concentration in vacuo, the residue was purified by silica gel column chromatography (ethylacetate/hexane/methanol = 4/4/1) to afford the title compound (26mg) in a yield of 42%.

[258] ¹H NMR (DMSO-d₆) δ ppm: 10.13 (1H, dd), 9.34 (1H, dd), 8.19 (1H, dd), 7.75 (3H, dd), 7.50 (1H, dd), 5.21 (1H, m), 4.87 (2H, dd), 4.31 (1H, dd), 3.97 (1H, dd)

[259] Example 22

[260] 1-(4-(R)-5-((1H-1,2,3-triazol-1-yl)methyl)-2-oxooxazolidin-3-yl)-2-fluorophenyl)-1H-1,2,3-triazole-4-carbaldehyde oxime(I-10)

[262] 1-[2-Fluoro-4-(2-oxo-5-[1,2,3]triazol-1-ylmethyl-oxazolidin-3-yl)-phenyl]-1H-[1,2,3]triazole-4-carbaldehyde (55mg, 0.15mmol), hydroxylamine hydrochloride (15mg, 0.23mmol) and potassium carbonate (32mg, 0.23mmol) were stirred in methanol/ dichloromethane (1:1) (2ml/2ml) for overnight. And then the resulting precipitate was collected, washed with water and dried under vacuum to yield 45mg (80%) of title compound.

[264] ¹H NMR (DMSO-d₆) δ ppm: 10.11 (1H, dd), 9.34 (1H, dd), 8.18 (1H, dd), 7.89 (1H, dd), 7.75 (2H, dd), 7.51 (1H, dd), 5.21 (1H, m), 4.87 (2H, dd), 4.31 (1H, dd), 3.97 (1H, dd)

[265] Example 23

[266] 1-(4-(R)-5-((1H-1,2,3-triazol-1-yl)methyl)-2-oxooxazolidin-3-yl)-2-fluorophenyl)-1H-1,2,3-triazole-4-carbonitrile(I-11)
[269] To a solution of the 1-[2-Fluro-4-(2-oxo-5-[1,2,3] triazol-
1-ylmethyl-oxazolidin-3-yl)-phenyl]-1H-[1,2,3]triazole-4-carbaldehyde oxime (45mg, 0.12mmol) and triethylamine (34μl, 0.24mmol) in dichloromethane (1ml), a solution of trichloroacetyl chloride (14μl, 0.13mmol) in dichloromethane (1ml) is added dropwise at 5–10°C. The mixture is allowed to reach room temperature and is stirred for 24h. The mixture was diluted with dichloromethane and washed with water. Drying (magnesium sulfate) and concentration in vacuo, the residue was purified by silica gel column chromatography (ethylacetate/hexane/methanol = 4/4/1) to afford the title compound (9mg) in a yield of 20%.

[270] ¹H NMR (DMSO-d₆) δ ppm: 9.55 (1H, dd), 8.18 (1H, dd), 7.89 (1H, dd), 7.79 (2H, dd), 7.53 (1H, dd), 5.21 (1H, m), 4.86 (2H, dd), 4.31 (1H, dd), 3.97 (1H, dd)

[271] **Example 24**

[272] **ethyl**

1-(4-((R)-5-((1H-1,2,3-triazol-1-yl)methyl)-2-oxooxazolidin-3-yl)-2-fluorophenyl)-1H
-pyrazole-4-carboxylate(I-12)

[273]

[274] Vinylacetate 12ml and ethyl

1-(4-((R)-5-(azidomethyl)-2-oxooxazolidin-3-yl)-2-fluorophenyl)-1H-pyrazole-4-carb oxylate (200mg, 0.53mmol) were heated to 110°C for 30h, followed by cooling and concentration in vacuo. The residue was purified by silica gel column chromatography (ethyl acetate/hexane/methanol = 6/6/1) to afford the title compound (184mg) in a yield of 86%.

[275] ¹H NMR (CDCl₃) δ 7.97-7.20 (7H, dd), 5.10 (1H, m), 4.72 (2H, dd), 4.69 (2H, q), 4.40 (1H, dd), 4.05 (1H, dd), 1.42 (3H, t)

[276] **Example 25**

[277] 1-(4-((R)-5-((1H-1,2,3-triazol-1-yl)methyl)-2-oxooxazolidin-3-yl)-2-fluorophenyl)-
1H-pyrrole-4-carboxamide(I-13)

[280]

A solution of the ethyl 1-(4-((R)-5-((1H-1,2,3-triazol-1-yl)methyl)-2-oxooxazolidin-3-yl)-2-fluorophenyl)-1H-pyrrole-4-carboxylate (184mg, 0.46mmol) and KCN (7.5mg, 0.115mmol) in saturated methanolic ammonia was heated in a sealed tube at 50°C. The solvent was evaporated and the residue was purified by silica gel column chromatography (ethyl acetate/hexane/methanol = 4/4/1) to afford the title compound (72mg) in a yield of 42%.

[282] \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 7.97-7.20 (7H, dd), 5.05 (1H, m), 4.70 (2H, dd), 4.32 (1H, dd), 4.09 (1H, dd)

[283]

Example 26

[284] 1-(4-((R)-5-((1H-1,2,3-triazol-1-yl)methyl)-2-oxooxazolidin-3-yl)-2-fluorophenyl)-1H-pyrrole-4-carbonitrile(I-14)

[286]

[287] 1-(4-((R)-5-((1H-1,2,3-triazol-1-yl)methyl)-2-oxooxazolidin-3-yl)-2-fluorophenyl)-1H-pyrrole-4-carboxamide (72mg, 0.19mmol) was placed in dry DMF 2.2ml and cooled to 0°C under N\(_2\). SOCl\(_2\) (21\(\mu\)l, 0.28mmol) was added dropwise and the reaction was stirred at room temperature for 30min. More SOCl\(_2\) (21\(\mu\)l, 0.28mmol) was added and stirring was continued another 30min. The mixture was extracted with methylene chloride, water and aq.NaHCO\(_3\). Drying (magnesium sulfate) and concentration in vacuo, the residue was purified by silica gel column chromatography (ethylacetate/hexane/methanol = 4/4/1) to afford the title compound (46mg) in a yield of 68%.

[288] \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 7.97-7.20 (7H, dd), 5.07 (1H, m), 4.74 (2H, dd), 4.34 (1H, dd), 4.05 (1H, dd)

[289]

Industrial Applicability
As described hereinbefore, the oxazolidinone derivatives of the general formula I have potent antibacterial activity against a broad spectrum of bacteria and their antibacterial activity is maintained high in vivo. Exerting potent antibacterial activity versus various human and animal pathogens, including gram-positive bacteria such as Staphylococi, Enterococci and Streptococi, anaerobic microorganism such as Bacteroides and Clostridia, and acid-resistant microorganism such as Mycobacterium, the compounds of the present invention are therefore useful as antibiotics.
Claims

[1] Derivatives of oxazolidinone of formula I, and pharmaceutically acceptable salt thereof:

[Formula I]

\[
\begin{align*}
\text{R} & \text{N} \quad \text{N} \\
\text{O} & \text{O} \\
\text{X} & \text{X}
\end{align*}
\]

wherein R is hydrogen atom, ethylcarboxylate, amide, diethoxymethyl, aldehyde, hydroxyoxime or nitrile;
X is each and independently carbon or nitrogen atom; and

---

is single bond or double bond.


[Formula 1-4]

\[
\begin{align*}
\text{R} & \text{N} \quad \text{N} \\
\text{O} & \text{O} \\
\text{X} & \text{X}
\end{align*}
\]

[Formula I]

\[
\begin{align*}
\text{R} & \text{N} \quad \text{N} \\
\text{O} & \text{O} \\
\text{X} & \text{X}
\end{align*}
\]

and pharmaceutically acceptable salt thereof.
wherein R is hydrogen atom, ethylcarboxylate, amide, diethoxymethyl, aldehyde, hydroxyoxime or nitrile;
X is each and independently carbon or nitrogen atom; and

---

is single bond or double bond.

[3] A method for preparing an oxazolidinone derivative of the general formula I which comprises reacting a compound of formula 2-4 with 2,5-dimethoxy-3-tetrahydrofurancarboxaldehyde using acetic acid, with sodium
azide using triethylorthoformate and also with sodium azide and vinylacetate.

[Formula 2-4]

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{N} \\
\text{F} & \quad \text{O} \\
\text{N} \quad \text{N} \quad \text{N} \\
\end{align*}
\]

[Formula I]

\[
\begin{align*}
\text{R} & \quad \text{X} \quad \text{X} \\
\text{F} & \quad \text{N} \\
\text{N} \quad \text{N} \quad \text{N} \\
\end{align*}
\]

and pharmaceutically acceptable salt thereof.

wherein R is hydrogen atom, ethylcarboxylate, amide, diethoxymethyl, aldehyde, hydroxyoxime or nitrile;

X is each and independently carbon or nitrogen atom; and

\[
\text{---}
\]

is single bond or double bond.
# International Search Report

**A. Classification of Subject Matter**

**IPC7 C07D 413/14**

According to International Patent Classification (IPC) or to both national classification and IPC

**B. Fields Searched**

Minimum documentation searched (classification system followed by classification symbols)

IPC7 C07D 413/14

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Korean Patents and applications for inventions since 1975.

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN(CASLINK)

**C. Documents Considered to be Relevant**

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