High-performance Liquid Chromatography Analysis of Mezlocillin, Piperacillin, their Degradation Products, and of Ioxitalamic Acid in Plasma and Urine of Healthy Volunteers

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Summary: In plasma and urine of 10 healthy volunteers after intravenous administration of 4 g mezlocillin and piperacillin, respectively, the parent compounds as well as degradation products were assayed by high-performance liquid chromatography. Ioxitalamic acid, a renal contrast medium, was administered simultaneously, in order to measure the glomerular filtration rate, and to control the collection of 24-h urine. As metabolite of mezlocillin the corresponding...
Zusammenfassung: Hochdruckflüssigkeitschromatographische Bestimmung von Mezlocillin, Piperacillin, ihrer Abbauprodukte und von Ioxitalamsäure im Plasma und Urin gesunder Probanden


Key words: Acylureidopenicillins • Diagnostics • Ioxitalamic acid, clinical pharmacokinetics • Mezlocillin, clinical pharmacokinetics • Piperacillin, clinical pharmacokinetics

1. Introduction

Mezlocillin (6-[[D-2-(2-oxo-3-mesylimidazolidine-1-carbox-amido)-2-phenylacetamido]penicillanic acid) and piperacillin (6-[D]-x-(4-ethyl-2,3-dioxo-1-piperazinyl-carbonyl-amin)-2-phenylacetamido] penicillanic acid) are acylureido penicillins with broad antibacterial activity and with only slight differences between their structures (Scheme 1). Penicillins are in general partially metabolized, mainly to inactive penicilloic acids [1]. This also was shown for mezlocillin, but in vitro degradation of mezlocillin in plasma samples may have influenced some results, leading to false high concentrations of mezlocillin penicilloic acids [3]. So far, no metabolites of piperacillin have been detected in plasma, though some inactive degradation products have been observed in urine and bile [2].

The aim of the present study was to establish the pharmacokinetics of mezlocillin and piperacillin after intravenous infusion of 4 g over 30 min, and to quantify their probable main metabolites, the corresponding penicilloic acids. For analysis a liquid chromatographic method was chosen instead of bioassay, because these ring-open penicillin derivatives are not antibacterially active. Care was taken with the sampling and storage of plasma samples because of in vitro instability of mezlocillin and other penicillins in body fluids [3].

2. Material and methods

2.1. Subjects

The study included 10 healthy subjects (5 male, 5 female, aged between 22 and 34 years, median 29 years). Their weights ranged between 50 and 86 kg (median 66 kg), and their heights between 154 and 188 cm (median 174 cm). The health of the volunteers was established from their medical history, physical examination and laboratory screening (differential blood count, platelet count, serum creatinine, SGOT, SGPT, GGT and urine analysis). No subject was hypersensitive to penicillins or contrast media. Pregnancy was excluded by the regular use of contraceptives.

2.2. Administration of antibiotics

After giving informed written consent the subjects received 4 g of mezlocillin and after 6 weeks 4 g of piperacillin. Concurrently, the subjects received 5 ml Tebelex 300°, equivalent to 2.4 g ioxitalamic acid, as an internal standard for comparison of the two antibiotics. The injection of this contrast medium allows to measure the renal function as glomerular filtration rate, and to control the collection of the 24-h urine. The antibiotics and ioxitalamic acid were dissolved together in 50 ml water for injections and infused intravenously within 30 min at a constant rate.
amido-N-(2-hydroxy-ethyl)-2,4,6-triiodo isophtalamic acid) were supplied by the respective manufacturers. As diagnostic agent megilumine oxitalamate (Telebrix 300®, manufacturer: Byk Gulden, Konstanz, FR Germany) was used. Acetonitrile (HPLC grade S) was purchased from Merck (Frankfurt/Main, FR Germany), tetradecylammonium hydrogensulfate from Fluka, Neu Ulm (FR Germany). All other chemicals (analytical grade) were obtained from E. Merck, Darmstadt (FR Germany). Water was purified with a Milli-Q water purification system (Millipore, Eschborn, FR Germany).

Stock solutions of the antibiotics, their metabolites and of oxitalamate were prepared in water to yield final concentrations of 1 mg/ml, and stored in aliquots at -20 °C. The stock solutions were then diluted with drug-free plasma to provide assay standards of 50 μg/ml for mezlocillin and piperacillin and 20 μg/ml for the penicilloic acids of both penicillins. For checking the linearity of the assay dilutions of 100-0.78 μg/ml for mezlocillin and piperacillin in plasma and 20-0.63 μg/ml for mezlocillin penicilloic acid were prepared. Lack of sufficient material did not allow to prepare a standard series of piperacillin penicilloic acid. For urine samples the standard solutions were prepared in 50 mmol/l sodium phosphate buffer (pH 6.5).

2.4.2. Sample treatment

Plasma samples were treated according to a published procedure [5] with minor modifications. In brief, 200 μl plasma were buffered with 200 μl 50 mmol/l sodium phosphate (pH 6.0) and deproteinized with 400 μl acetonitrile. The latter was then extracted into 2 ml methanol containing 10-200 μg/ml 6-sila (the aqueous phase, containing the penicillins and their metabolites, were injected into the chromatograph. Urine was centrifuged and diluted tenfold with 50 mmol/l sodium phosphate buffer (pH 6.5). All biological samples were stored at -70 °C (up to 7 weeks) and thawed in iced water just prior to analysis.

2.4.3. Chromatography

The chromatographic system consisted of a pump M 6000A, an automatic injector WISP 710B (fitted with a cooling kit, in order to maintain 8 °C for the samples), a RCISS compression module equipped with a cartridge (100 x 5 mm I.D.) packed with Novapak® C-18 4.5 μm silica, a fixed-wavelength detector M 441, a data module M 730 and a system controller M 720 (all from Waters Assoc., Eschborn, FR Germany).

The flow rate was maintained at 1.0 ml/min, the resulting back-pressure was 6000 kPa. The eluent was monitored at 214 nm (Zn-lamp) for the determination of mezlocillin and at 229 nm (Cd-lamp) for the determination of piperacillin. For mezlocillin analysis the mobile phase was prepared by combining 760 ml of 12.5 mmol/l sodium phosphate buffer (pH 6.8), 240 ml acetonitrile and 150 mg tetrabutylammonium hydrogen sulphate. The pH value was adjusted to 7.3 with 10 N sodium hydroxide. Part of the mezlocillin samples was analysed using a HIBAR® column (125 x 4 mm I.D.) filled with LiChrosphere® silica (E. Merck; for mobile phase composition see Fig. 1). For piperacillin assay a g tetrabutylammonium hydrogen sulphate was used and the pH adjusted to 6.5.

For determination of oxitalamate a HIBAR column (125 x 4 mm I.D.), prepacked with LiChrosphere® RP-18 5 μm silica (E. Merck), was used for separation. The flow rate was maintained at 1.0 ml/min, the back-pressure was 11000 kPa. The mobile phase was a mixture of 910 ml water, 90 ml acetonitrile, 600 μl acetic acid, 150 mg tetrabutylammonium hydrogen sulphate. The pH value was adjusted to 4.8 with 10 N sodium hydroxide. The eluent was monitored at 254 nm (Hg-lamp), the retention time of oxitalamic acid was about 4.5 min.

2.4.4. Pharmacokinetic analysis

Plasma level data were analysed by the open, two-compartment model. The decline in drug plasma levels in the postinfusion phase was fitted to a computer program for each subject using an iterative least-squares regression analysis. A Fortran program was used in the computation. The basic equation of the mathematical model was:

\[ C_t = A \cdot e^{-\alpha t} + B \cdot e^{-\beta t} \]

where \( C_t \) represents the plasma concentrations at time \( t \) after the dose. \( \alpha \) and \( \beta \) (min\(^{-1}\)) are hybrid constants of the fast and the slow disposition process, respectively, and \( A \) and \( B \) (mg/l) are the zero-time intercepts of the two components of the biexponential curve.

The calculated pharmacokinetic constants were corrected for infusion time [6]. A number of parameters have been calculated, especially following: area under the plasma concentration-time curve (AUC₁₋₂), apparent steady-state volume of distribution (VSS), total body clearance (CL₀), and terminal plasma half-life (t₁/2).

3. Results

3.1. Chromatography

In Fig. 1 chromatograms of a standard mixture of mezlocillin and its degradation products, mezlocillin penicilloic acid, and of extracted human plasma are depicted. Each mezlocillin metabolite elutes at two distinct peaks because of epimerization at the carbon atom in position 5 (see Scheme 1) [7]. The earlier eluting isomers A are the minor components in freshly prepared aqueous solutions, but become dominant when standing at room temperature for many hours as it was also described for amoxycillin penicilloic acid [8]. In plasma and urine, we found mezlocillin penicilloic acid and its degradation products from interfering plasma components, and run time was found with 255 mg/l tetrabutylammonium hydrogen sulphate, 750 ml water, 250 ml acetonitrile, apparent pH 6.2; flow rate: 1 ml/min; pressure 11000 kPa.

3.2. Evaluation of the assay

The chromatographic peaks were quantitated by the area method. The areas of the two unidentified metabolites of pi-
Fig. 2: Chromatograms of (1) an aqueous standard solution of piperacillin (PIP, 250 ng) and piperacillin penicilloic acid (PPC, ca. 200 ng mixture of epimers A and B; the asterisk marks an impurity, presumably a hydrolysis product of piperacillin), (2) a plasma blank, (3) plasma of a volunteer 1 h and (4) 4 h after the end of an intravenous infusion (30 min) of 4 g piperacillin. X marks two unidentified peaks (A and B), probably a mixture of epimers. Concentrations: (3) PIP = 47 µg/ml, PPC = 23 µg/ml, X = 9.8 µg/ml when quantified as PIP. (4) PIP = 2.6 µg/ml; X = 4.8 µg/ml. Chromatographic conditions: see Material and methods. AU = absorption units.

Fig. 3: Concentration-time course of mezlocillin (●), mezlocillin penicilloic acid (○) and of ioxitalamic acid (■) (mean, SD) after intravenous infusion (30 min) of 4 g mezlocillin and 2.4 g ioxitalamic acid to 10 healthy volunteers.

Fig. 4: Concentration-time course of piperacillin (●), piperacillin penicilloic acid (○), compound X (■), and of ioxitalamic acid (■) (mean, SD) after intravenous infusion (30 min) of 4 g piperacillin and 2.4 g ioxitalamic acid in 10 healthy volunteers.

Fig. 5: Cumulative urinary recovery (mean, SD) of mezlocillin (●) and mezlocillin penicilloic acid (○) in 10 healthy volunteers after intravenous infusion (30 min) of 4 g mezlocillin.

Fig. 6: Cumulative urinary recovery (mean, SD) of piperacillin (●) piperacillin penicilloic acid (○), and of compound X (■) in 10 healthy volunteers after intravenous infusion (30 min) of 4 g piperacillin. □ = Sum of ■ and □.
peracillin were summarized and quantified as piperacillin. The recovery from plasma was 101.1 ± 1.3% for mezlocillin (concentration 100 µg/ml; n = 9), for mezlocillin penicilloic acid 100.8 ± 2.8% (concentration 42 µg/ml; n = 9), for piperacillin 104.3 ± 4.0 (concentration 50 µg/ml; n = 15) and for piperacillin penicilloic acid 91 to 93% (concentration 20 µg/ml; n = 3). The recovery from urine was not checked and set 100%, as the only sample treatment step was dilution of urine with buffer.

Some plasma specimens of the mezlocillin study were determined at two different days and the following reproducibility was found: mezlocillin 102.7 ± 4.8% (concentration range 0.80 to 3.6 µg/ml), mezlocillin penicilloic acid 107 ± 20% (concentration range 0.80 to 3.6 µg/ml). The precision of the piperacillin assay was checked with spiked plasma. The results are shown in Table 1.

### 3.3. Pharmacokinetics

Fig. 3 and 5 show the mean (± SD) plasma concentrations and the cumulative urinary excretion of mezlocillin and its ring-open metabolite. Fig. 4 and 6 the respective data of piperacillin. In addition, the plasma concentrations of ioxitalamic acid are depicted. In both cases, the mean plasma concentrations of the metabolites were always much lower than the values of the respective parent compounds. Apparently neither mezlocillin nor piperacillin is metabolized in vivo to a greater extent. These findings are also illustrated in Table 2. In both studies we found nearly identical values for ioxitalamic acid in plasma, and in the beginning also for mezlocillin and piperacillin. With the time elapsed, the concentrations of mezlocillin remained slightly higher than those of piperacillin.

The pharmacokinetic parameters of mezlocillin, piperacillin, and of ioxitalamic acid are summarized in Table 3. All substances exhibit distribution volumes nearly 20% of body weight which agrees good with the extracellular space. Like ioxitalamic acid [9], ioxitalamic acid shows the same plasma clearance as inulin (ca. 120 ml/min), whereas those of mezlocillin and piperacillin are about 250 ml/min. On the other hand, the half-life of ioxitalamic acid in plasma is about 2 h, whereas the half-lives of both antibiotics are 1 h. The urinary recovery of ioxitalamic acid within 24 h was 90% in each study so that complete 24-h urine collection can be assumed. Also the excretion of creatinine was normal in all subjects. About 50% of the antibiotic doses given were recovered in the urine as active parent compounds, and 9% as metabolites in the case of piperacillin and 4% in the case of mezlocillin.

### 4. Discussion

#### 4.1. Chromatographic assay

Besides the traditional bioassay, mezlocillin and piperacillin have been also determined in biological fluids by reversed phase HPLC [10–15]. But in all these cases the parent compounds only were assayed, as the ring-open metabolites are much more polar and elute with the front. Using gradient elution technique mezlocillin [16], azlocillin [17], apacillin [18], and the respective penicilloic acids could be determined simultaneously in serum and urine. Unfortunately, all assays are considerably time consuming. In the present assay incorporation of ion-pair chromatography enabled iso-

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**Table 1:** Precision of the determination of piperacillin in plasma. (Piperacillin added: 25, 5, 0.5 µg/ml.)

<table>
<thead>
<tr>
<th>Day</th>
<th>Piperacillin (µg/ml)</th>
<th>Mean SD (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25.2</td>
<td>5.69</td>
</tr>
<tr>
<td>2</td>
<td>26.0</td>
<td>5.85</td>
</tr>
<tr>
<td>3</td>
<td>25.3</td>
<td>5.29</td>
</tr>
<tr>
<td>4</td>
<td>26.1</td>
<td>5.96</td>
</tr>
<tr>
<td>5</td>
<td>26.2</td>
<td>5.74</td>
</tr>
</tbody>
</table>

**Table 2:** Mean (± SD) concentrations of mezlocillin and piperacillin after infusion (30 min) of 4 g. and of simultaneously administered ioxitalamic acid (2.4 g) in plasma of ten healthy volunteers. ITXpip = ioxitalamic acid in the piperacillin study; ITXmez = ioxitalamic acid in the mezlocillin study; MEZ = mezlocillin; PIP = piperacillin.

<table>
<thead>
<tr>
<th>Time</th>
<th>ITXpip (µg/ml)</th>
<th>ITXmez (µg/ml)</th>
<th>ITXpip (µg/ml)</th>
<th>MEZ (µg/ml)</th>
<th>PIP (µg/ml)</th>
<th>MEZ/Pip (100 %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 min</td>
<td>141 ± 27</td>
<td>134 ± 26</td>
<td>95.0</td>
<td>200 ± 58</td>
<td>198 ± 42</td>
<td>110.0</td>
</tr>
<tr>
<td>10 min</td>
<td>194 ± 31</td>
<td>187 ± 24</td>
<td>96.4</td>
<td>271 ± 61</td>
<td>272 ± 75</td>
<td>99.6</td>
</tr>
<tr>
<td>10 min</td>
<td>126 ± 66</td>
<td>121 ± 27</td>
<td>101.4</td>
<td>198 ± 46</td>
<td>187 ± 33</td>
<td>105.9</td>
</tr>
<tr>
<td>10 min</td>
<td>110 ± 15</td>
<td>108 ± 24</td>
<td>104.3</td>
<td>158 ± 39</td>
<td>148 ± 26</td>
<td>99.8</td>
</tr>
<tr>
<td>10 min</td>
<td>94.9 ± 15.9</td>
<td>91.3 ± 17.9</td>
<td>98.7</td>
<td>129 ± 34</td>
<td>118 ± 26</td>
<td>109.3</td>
</tr>
<tr>
<td>10 min</td>
<td>75.9 ± 11.5</td>
<td>78.5 ± 16.0</td>
<td>97.6</td>
<td>97.7 ± 25.8</td>
<td>87.7 ± 22.5</td>
<td>111.4</td>
</tr>
<tr>
<td>10 min</td>
<td>63.9 ± 5.9</td>
<td>61.0 ± 12.2</td>
<td>96.2</td>
<td>73.0 ± 21.8</td>
<td>65.2 ± 14.5</td>
<td>112.0</td>
</tr>
<tr>
<td>10 min</td>
<td>49.3 ± 9.4</td>
<td>49.2 ± 10.8</td>
<td>99.8</td>
<td>45.1 ± 16.5</td>
<td>39.6 ± 11.2</td>
<td>113.9</td>
</tr>
<tr>
<td>10 min</td>
<td>32.0 ± 8.2</td>
<td>32.0 ± 7.5</td>
<td>100.0</td>
<td>29.5 ± 13.4</td>
<td>24.1 ± 8.4</td>
<td>122.4</td>
</tr>
<tr>
<td>10 min</td>
<td>22.1 ± 6.0</td>
<td>21.1 ± 6.9</td>
<td>95.5</td>
<td>12.5 ± 4.7</td>
<td>11.5 ± 5.8</td>
<td>108.7</td>
</tr>
<tr>
<td>10 min</td>
<td>10.4 ± 3.0</td>
<td>9.6 ± 3.9</td>
<td>92.3</td>
<td>1.6 ± 0.8</td>
<td>1.5 ± 0.6</td>
<td>106.7</td>
</tr>
<tr>
<td>10 min</td>
<td>5.1 ± 2.3</td>
<td>5.0 ± 2.4</td>
<td>98.0</td>
<td>0.6 ± 0.4</td>
<td>0.6 ± 0.2</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Mean ± SD 98.0 ± 3.1 108.2 ± 6.2

1) 15 min after the start of infusion (the antibiotics were infused at a constant rate over 30 min).

2) At the end of infusion.

**Table 3:** Comparative pharmacokinetic parameters (mean ± SD) of mezlocillin (4 g), piperacillin (4 g), and simultaneously administered ioxitalamic acid (2.4 g) given as short intravenous infusion (30 min) to 10 healthy volunteers. Abbreviations: ITXmez = ioxitalamic acid in the mezlocillin test; ITXpip = ioxitalamic acid in the piperacillin test; MEZ = mezlocillin; PIP = piperacillin; Vss = steady-state volume of distribution; AUC = area under the plasma concentration-time curve; Clb = total body clearance; t1/2 = terminal plasma half-life; Vss% b.w. = Vss in percentage of body weight; Clb 24 h = Clb normalized to 70 kg body weight; Uo-24 h = 24-h urinary recovery.

<table>
<thead>
<tr>
<th>Vss (l)</th>
<th>Vss% b.w. (%)</th>
<th>AUC (mg/l h)</th>
<th>Clb (ml/min)</th>
<th>Clb 70 kg (ml/min/70 kg)</th>
<th>t1/2 (min)</th>
<th>Uo-24 h (µg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITXmez</td>
<td>15.5 ± 3.2</td>
<td>23.5 ± 3.6</td>
<td>349 ± 71</td>
<td>118 ± 27</td>
<td>127 ± 27</td>
<td>106 ± 15</td>
</tr>
<tr>
<td>ITXpip</td>
<td>15.2 ± 2.6</td>
<td>23.3 ± 4.5</td>
<td>359 ± 59</td>
<td>114 ± 18</td>
<td>123 ± 27</td>
<td>107 ± 14</td>
</tr>
<tr>
<td>MEZ</td>
<td>14.3 ± 3.8</td>
<td>21.8 ± 5.1</td>
<td>303 ± 76</td>
<td>231 ± 30</td>
<td>247 ± 52</td>
<td>63.9 ± 10</td>
</tr>
<tr>
<td>PIP</td>
<td>14.5 ± 2.7</td>
<td>21.2 ± 4.7</td>
<td>283 ± 61</td>
<td>240 ± 50</td>
<td>262 ± 54</td>
<td>66.4 ± 13</td>
</tr>
</tbody>
</table>

1) 24-h creatinine excretion: mezlocillin study (1801 ± 330 mg (male): 1215 ± 609 (female)). Piperacillin study (2102 ± 130 mg (male), 1309 ± 412 (female)).

2) In addition: 4.1 ± 1.0% as mezlocillin penicilloic acid, and 5.0 ± 1.5% as compound X.
cratic determination of mezlocillin, piperacillin, and their probable main metabolites within 10 min at a moderate flow rate. From the present investigation it results that mezlocillin and piperacillin are degraded only to a very small extent to the respective penicilloic acids after intravenous injection (Fig. 3 and 4). Moreover, it seems doubtful whether the measured concentrations of the penicilloic acids are caused by enzymatic metabolism, or mainly by mere chemical hydrolysis. The instability of these and other penicillins in standing plasma specimens was several times reported, and even at -18°C 20% degradation of mezlocillin in plasma within 6 weeks was observed, whereby half of it was found in form of mezlocillin penicilloic acid [3]. Therefore, the detection of large amounts of mezlocillin penicilloic acid in any body fluid specimen may indicate rather in vitro degradation of the parent compound than in vivo metabolism. In such cases, false low concentrations of mezlocillin are measured, and determination of degradation products can prove it (cf. [3]). In accordance with results examined by Gau and Förster [16] we did not find mezlocillin penicilloic acid in plasma and urine, and indeed, the detection of penicilloic acid in body fluids [19] may have been an artefact of the analytical procedure [3].

Even quantitative disappearance of piperacillin from plasma specimens was stated when stored for several weeks at -20°C ([10]; unfortunately, though HPLC was used, no attempt was made to look for degradation products). On the other hand, at -70°C both antibiotics proved to be stable [3, 10]. In our study, all specimens were stored at -70°C no longer than 7 weeks so that stability of piperacillin should be guaranteed. Moreover, we found only small amounts of piperacillin penicilloic acid, the supposed main degradation product in stored plasma. But beyond that, two unidentified signals appeared in the chromatograms of plasma and urine (Fig. 2, chromatograms 3 and 4, peaks X-A and X-B).

On following reasons we believe the signals may refer to 6-[D(-)-β-[[3-[(N-ethyl-N-oxalamino)ethyl]ureido]-β-phenylacetylamido] penicilloic acid (Scheme 1), denoted X in Fig. 1, which is partially epimerized at the carbon atom in position 5, and elutes therefore as two distinct peaks. First, the peak/height ratio 229 to 254 nm (Fig. 2) of X-A and X-B is similar to those of piperacillin and piperacillin penicilloic acid which fits the proposed structure. Second, with time the relative amount of the faster eluting peak increases in accordance with findings in the case of the penicilloic acids of mezlocillin and apacillin [18]; unfortunately, piperacillin penicilloic acid was hardly to quantify in plasma, all the more since the isomer A was often covered by an endogenous compound. Third, the same splitting of the dioxopiperazine ring was found in the case of cefoperazone [20]. The Bateman-function-like concentration-time course of compound X in plasma (Fig. 4) demonstrates it to be formed in vivo, presumably as a metabolite of piperacillin penicilloic acid. However, the identity of the compounds X-A and X-B remains to be elucidated.

4.2. Comparative pharmacokinetics of mezlocillin and piperacillin

The study was not designed in a randomised cross-over fashion but the analysis of the pharmacokinetic parameters of ioxitalamic acid in both tests (Table 3) revealed nearly identical mean values so that similar conditions can be assumed to exist for both antibiotics mezlocillin and piperacillin. All their meta-pharmakokinetic parameters differed not more than 10% from each other which is within the analytical error, and in accordance with published data [21, 22]. We observed also the same urinary recovery of both antibiotics, about half of the dose given, which was to be expected for mezlocillin only [3, 16, 21]. Tjandramaga [22] found 80% of piperacillin in the urine when a 4 g intravenous dose was given. This is in clear contrast to our results. On the other hand, a range of 40—70% renal excretion of piperacillin is also reported [23, 24]. So, for piperacillin in a very large range of renal excretion is found. Our data are at its lower margin, but in good agreement with the renal excretion of the other acylureido penicillins, mezlocillin [3, 16, 21] and azlocillin [17], which exhibit very similar chemical structures.

5. References


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