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# Synthetic β-Lactam Antibiotics VII. Antibacterial Activity of Some 7β-[(Z)-(2-Aminothiazol-4-yl)-2-(methoxyimino)acetamido]-3-(1-azabicyclo[2.2.1]heptanio] methylcephalosporins

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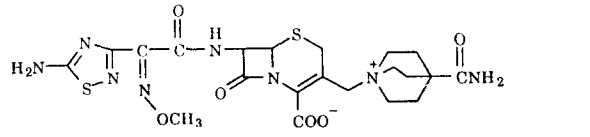
Cefclidin (**1**)(Sugiyama *et al.*, 1992) having a quinuclidine derivative at the C-3 position of cephem nucleus, newly developed by Eisai Co., exhibits high stability to β-lactamases as well as excellent activity against both Gram-positive and Gram-negative bacteria. In our continuous efforts to develop highly active cephalosporins, we were interested in the synthesis of 1-azabicyclo[2.2.1]heptane derivative which is similar in structure with quinuclidine but lacking in one carbon atom. Thus we wished to investigate the effect of 1-azabicyclic ring on antibacterial potency and efficacy. In this study we report the synthesis, structure-activity relationships and biological property of cephalosporins having a 1-azabicyclic derivative in the C-3 side chain.

3-Oxo-1-azabicyclo[2.2.1]heptane (**3a**) was prepared from dimethyl itaconate by the reported method(Street *et al.*, 1990). The compounds **3b-3d** were synthesized from **3a** using the proper reaction conditions such as reduction with Pd/H2, acetolysis or reaction with hydroxylamine. Treatment of 7-benzyl-7-aza-2-oxaspiro[4, 4]nonan-1-one, prepared from 2-methylene-γ-butyrolactone, with HBr, followed by debenzylation reaction to afford ethyl 1-azabicyclo[2.2.1]heptane-4-carboxylate **3e** (Jenkins *et al.*, 1992). The compound **3e** was hydrolyzed or aminated to give **3f** or **3g** in a good yield. The new cephalosporins **4a-4g** tested were prepared as shown in Scheme 1. Cefotaxime (**2**) was silylated and iodized, then reacted with azabicyclo compounds **3a-3g** to give the corresponding cephalosporins in reasonable yields(Albrecht *et al.*, 1991). The NMR spectra were recorded on Varian Gemini 300 MHz spectrometer using TMS as an internal standard and the result is shown in Table I.

The in vitro antibacterial activity of compounds **4a-4g** was determined by the standard two fold agar dilution method. Minimum Inhibitory concentrations(MICs) of these compounds against 20 selected strains of bacteria are listed in Table II along with cefotaxime as a reference compound. These new cephalosporins exhibited fairly potent and broad activities against Gram-positive and Gram-negative bacteria ranging from 0.007 to 6.25 μg/ml for the MIC except against *Streptococcus faecium* MD 8b. Against Gram-negative organism these compounds showed comparable activity with cefotaxime and higher antipseudomonal activity. This result is usually detected with cephalosporins having a quaternary ammoniomethyl group at the C-3 side chain due to increasing cell wall penetration with increasing hydrophilicity. Among 3 compounds having



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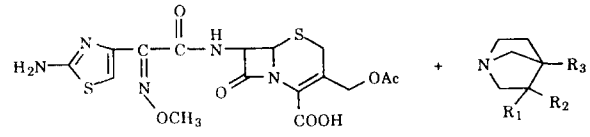

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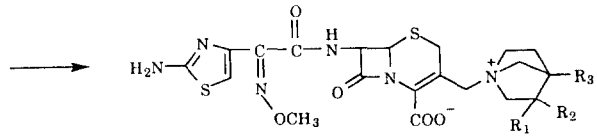

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| | $R_1$ | $R_2$ | $R_3$ |
|---|---|---|---|
| a | =O | | H |
| b | OH | H | H |
| c | $OCOCH_3$ | H | H |
| d | =N-OH | | H |
| e | H | H | $CO_2Et$ |
| f | H | H | $CO_2H$ |
| g | H | H | $CONH_2$ |

**Scheme 1**

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**Table I.** NMR spectral data in DMSO-$d_6$ of cephalosporins

| Compound No. | 3-$CH_2$ (2H, ABq J=14H) | 6-H (1H, d J=8H) | 7-H (1H, dd J=5H, 8H) | −CONH− (1H, d J=8H) | −$OCH_3$ (3H, s) | Thiazole (1H, s) | Other protons |
|---|---|---|---|---|---|---|---|
| **4a** | 4.63 | 5.26 | 5.89 | 9.65 | 3.85 | 6.75 | 3.50~4.30(m)<br>2.07~2.08(1H, m)<br>1.85~1.95(1H, m) |
| **4b** | 4.43 | 5.27 | 5.88 | 9.65 | 3.85 | 6.75 | 4.50(1H, brs)<br>4.20~4.30(1H, m)<br>2.80~4.0(m)<br>2.10~2.35(1H, m)<br>1.90~2.10(1H, m) |
| **4c** | 4.46 | 5.23 | 5.86 | 9.64 | 3.84 | 6.74 | 5.13~5.20(1H, m)<br>3.10~4.10(m)<br>2.0~2.25(2H, m)<br>2.08(3H, s) |
| **4d** | 4.56 | 5.26 | 5.89 | 9.66 | 3.85 | 6.75 | 3.50~4.50(m)<br>2.71~2.73(1H, m)<br>2.30~2.45(1H, m)<br>1.85~1.95(1H, m) |
| **4e** | 4.50 | 5.26 | 5.87 | 9.64 | 3.84 | 6.74 | 4.15~4.20(2H, q)<br>3.20~3.80(m)<br>2.30~2.40(2H, m)<br>2.0~2.10(2H, m)<br>1.25(3H, t) |
| **4f** | 4.49 | 5.22 | 5.85 | 9.63 | 3.85 | 6.75 | 3.10~4.30(m)<br>2.30~2.40(2H, m)<br>2.0~2.20(2H, m) |
| **4g** | 4.47 | 5.25 | 5.88 | 9.64 | 3.85 | 6.74 | 3.30~4.0(m)<br>2.20~2.32(2H, m)<br>2.0~2.15(2H, m) |

**Table II.** In vitro antibacterial activity (MIC, μg/ml) of cephalosporins

| Organism | **4a** | **4b** | **4c** | **4d** | **4e** | **4f** | **4g** | Cefotaxime |
|---|---|---|---|---|---|---|---|---|
| *Streptococcus pyogenes* 308 | 0.025 | 0.025 | 0.025 | 0.013 | 0.013 | 0.098 | 0.013 | 0.013 |
| *Streptococcus pyogenes* 77A | 0.013 | 0.007 | 0.013 | 0.007 | 0.007 | 0.049 | 0.007 | 0.007 |
| *Streptococcus faecium* MD 8b | 100 | 100 | 100 | 100 | >100 | >100 | 100 | 50 |
| *Staphylococcus aureus* SG 511 | 3.125 | 3.125 | 6.25 | 3.125 | 6.25 | 50 | 3.125 | 1.563 |
| *Staphylococcus aureus* 285 | 6.25 | 6.25 | 6.25 | 12.5 | 25 | >100 | 25 | 1.563 |
| *Staphylococcus aureus* 503 | 1.563 | 1.563 | 3.125 | 1.563 | 1.563 | 25 | 1.563 | 1.563 |
| *Escherichia coli* 055 | 0.049 | 0.049 | 0.049 | 0.025 | 0.049 | 0.098 | 0.013 | 0.013 |
| *Escherichia coli* DC 0 | 0.098 | 0.098 | 0.098 | 0.049 | 0.098 | 0.098 | 0.098 | 0.049 |
| *Escherichia coli* DC 2 | 0.098 | 0.098 | 0.098 | 0.049 | 0.098 | 0.195 | 0.025 | 0.013 |
| *Escherichia coli* TEM | 0.098 | 0.098 | 0.098 | 0.049 | 0.098 | 0.391 | 0.049 | 0.025 |
| *Escherichia coli* 1507E | 0.049 | 0.049 | 0.098 | 0.049 | 0.098 | 0.098 | 0.025 | 0.049 |
| *Pseudomonas aeruginosa* 9027 | 6.25 | 6.25 | 12.5 | 6.25 | 25 | 50 | 6.25 | 25 |
| *Pseudomonas aeruginosa* 1592E | 3.125 | 3.125 | 6.25 | 3.125 | 12.5 | 50 | 6.25 | 12.5 |
| *Pseudomonas aeruginosa* 1771 | 1.563 | 1.563 | 3.125 | 3.125 | 6.25 | 12.5 | 3.125 | 6.25 |
| *Pseudomonas aeruginosa* 1771M | 0.195 | 0.195 | 0.39 | 0.098 | 0.391 | 0.781 | 0.098 | 0.098 |
| *Salmonella typhimurium* | 0.098 | 0.049 | 0.098 | 0.049 | 0.098 | 0.195 | 0.025 | 0.025 |
| *Klebsiella oxytoca* 1082E | 1.563 | 1.562 | 1.563 | 1.563 | 1.563 | 12.5 | 1.563 | 0.781 |
| *Klebsiella aerogenes* 1522E | 0.049 | 0.049 | 0.098 | 0.049 | 0.049 | 0.098 | 0.025 | 0.025 |
| *Enterobacter cloacae* P99 | 3.125 | 6.25 | 6.25 | 6.25 | 12.5 | >100 | 6.25 | 12.5 |
| *Enterobacter cloacae* 1321E | 0.013 | 0.025 | 0.025 | 0.013 | 0.013 | 0.049 | 0.007 | 0.007 |

4-substituted azabicyclic ring in the C-3 side chain **4g** exhibited somewhat higher activity in comparison to the other two compounds. It was presumed that a carbamoyl group on azabicyclic ring more influenced the antibacterial activity compared to other functional groups. This effect was also observed in case of cefclidin and in this lab with the previous work (Lim *et al.*, 1992). For 3-substituted azabicyclic ring derivatives there was no perceptible difference in effect on the biological activity among functional groups. Further derivatization of azabicyclic ring and evaluation of the new compounds are in progress.

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