Journal of Food and Drug Analysis

Volume 6 | Issue 2 Article 5

1998

Methods in the preparation of D-phenylglycine-containing cefotaxime double esters

Journal of Food and Drug Analysis
1998. 6(2) : 477-484

Methods in the Preparation of D-Phenylglycine-containing Cefotaxime Double Esters

CHI-HUA SUN AND HUI-PO WANG*

School of Pharmacy, National Taiwan University 1. Sec 1, Jen-ai Rd., Taipei, Taiwan 100, Republic of China

ABSTRACT

Alkylation of cefotaxime sodium with 1-iodoethyl 2-N(Boc)-D-phenylglycine (3a and 3b) led to double esters 4a, 4b where the carboxyl group of D-phenylglycine was linked to the 4-carboxyl group of cefotaxime via an ethyledine moiety, and their Δ^2 isomeric analogues 5a and 5b. The $\Delta^3 \rightarrow \Delta^2$ isomeric transformation from 4a and 4b to 5a and 5b during the synthesis was successfully eliminated by the addition of TBA+HSO_4^- to the reaction media. Hydrolysis of the mixture of 4a and 4b followed by medium pressure liquid chromatographic separation afforded the D-phenylglycine-containing double ester prodrugs of cefotaxime (1a and 1b). Compounds 1a and 1b were stable in acidic phosphate buffer solution, but were degraded fairly rapidly in a pH 7. 39 phosphate buffer solution. The $t_{1/2}$ of 1a and 1b in a mucosal suspension prepared from rat intestine were 11 minutes and 1 minute respectively. These two compounds failed to demonstrate satisfactory stability for formulation as oral prodrugs of cefotaxime.

Key words: **cefotaxime prodrugs, tetrabutylammonium hydrogen sulfate, D-phenylglycine.**

INTRODUCTION

Cefotaxime is one of the third generation cephalosporins with a potent broad spectrum of activity against important pathogens[1-5] such as *Streptococcus pneumoniae meningitis*[6,7]. It is considered one of the first choice antibiotics in the therapy of spontaneous bacterial peritonitis in cirrhosis[8,9]. The drug is administered mainly by injection due to its poor degree of oral absorption. In consequence of its small volume of distribution, low degree of protein binding and high hydrophilicity, this drug is characterized as a drug of fast renal elimination with short biological half life (1.0 hour)[10].

Studies revealed that a certain dipeptide transport system (DTS) exists in the intestine. The transporter showed broad specificity with less structural requirement for substrates[11,12]. Several amino-β-lactams, structurally as tripeptides, are absorbed via the system[13-15]. Interestingly, most of the orally absorbed amino-β-lactams have D-phenylglycine or D-*p*-hydroxyphenylglycine as common moieties in the molecules. Our previous studies indicated that D-phenylglycine is a useful tool for delivering hydrophilic drugs via this

Correspondence to: Hui-Po Wang

Accepted for Publication: Apr. 22, 1998

transport system[16-18]. We thus used D-phenylglycine for the preparation of compounds 1a and 1b as oral prodrugs of cefotaxime. This report describes the synthesis of the double ester compounds 1a and 1b. A method for the prevention of isomerization during the alkylation of cefotaxime is also reported. As oral administration of the prodrugs was desired, the stability of the compounds in phosphate buffer solutions and toward intestinal enzymatic degradation was investigated[19].

MATERIALS AND METHODS

I. *Materials and Instruments*

Cefotaxime sodium was kindly supplied by Gentle Pharmaceutical Cooporation Ltd.. Solvents and reagents were commercial products from E. Merck, Aldrich, Wako or Kasai Companies. HPLC grade acetonitrile (CH_3CN) was purchased from Alpus Chemical Company. The MPLC system consisted of a Buchi 681 pump, a Borosilicate 3.3 column, and a UA5 Absorbance/ Fluorescence detector. Melting points were determined on a Buchi 510 capillary melting point apparatus and were uncorrected. Spectral data were obtained from a Perkin-Elmer 1760 FT-IR spectrophotometer, Jeol JNS-D300 EI or CI mass spectrometer, Brucker 200 MHz or 400 MHz NMR spectrophotometer. Male Wistar rats weighing 200 - 350 g were used to prepare the intestinal mucosal suspension.

II. *Synthesis*

(I) *1-(t-Butyloxycarbamoyl-D-phenylacetyloxy)-1-ethyl [6R-[6α,7β(Z)]]-3-[(acetoxy)methyl]-7-[[(2-amino-4-thiazolyl) (methoxyimino) acetyl] amino]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate (4a and 4b)*

A mixture of 1-chloroethyl-N(Boc)-D-phenylglycine (2a and 2b, 3.76 g, 12 mmol)[20] and NaI (18.00 g, 0.12 mol) in CH_3CN (150 ml) was stirred at room temperature for 48 h. CH_3CN was removed in vacuo. The residue was extracted with CH_2Cl_2 (50 ml) and filtered. The filtrate was concentrated to dryness. NMR spectrum indicated that 55% of the starting material was converted to the iodo intermediates 3a and 3b. The mixture was dissolved in DMF (150 ml) and allowed to react with cefotaxime sodium (2.86 g, 6.00 mmol) in the presence of $TBA+HSO_4^-$ (2.04 g, 6.00 mmol) at 0 ℃ for 25 min. DMF was removed in vacuo. The residue was partitioned between EtOAc (150 ml) and water (150 ml). The organic layer was separated, washed first with aqueous 0.1N HCl solution (150 ml) and then with saturated brine. The solution was dried over $MgSO_4$ and concentrated in vacuo. The oily residue was chromatographed with MPLC (silica gel, 15-40 μm, 100 g) using EtOAc : n-hexane = 3 : 1 (v/v) as the eluent to give 1.01 g (24 %) of the diastereomeric products 4a and 4b, identified as a mixture in a ratio of 1 to 1; mp 120-123 ℃, IR (KBr) 2980, 1780, 1740, 1720, 1620, 1530, 1380, 1360, 1220, 1160, 1070 cm^{-1}, ^1H NMR (400 MHz, $CDCl_3$): δ 1.42, 1.52 (3H, *dx2*, *J* =*5.4 Hz*, -CHC<u>H</u>$_3$), 2.05 (3H, *s*, -CH_2OCOC<u>H</u>$_3$), 3.42, 3.50 (2H, AB*qx2*, *J* =*18.7 Hz*, 2-H), 4.03, 4.05 (3H, *sx2*, -NOC<u>H</u>$_3$), 4.72 (1H, *s*, D-phenylglycine-α-H), 4.80, 5.12 (2H, ABq, *J* =*13.6 Hz*, -C<u>H</u>$_2$OCOCH_3), 4.96, 5.07 (1H, *dx2*, *J* = *4.5 Hz*, 6-H), 5.29, 5.95 (2H, *sx2*, -NH_2), 5.42, 5.73 (1H, *mx2*, -N<u>H</u>(Boc)), 5.97, 6.12 (1H, *mx2*, 7-H), 6.70, 6.78 (1H, *sx2*, thiazole-H), 6.97, 7.09 (1H, *mx2*, -C<u>H</u>CH_3), 7.33 (5H, *m*, ArH), 7.81, 8.29 (1H, *mx2*, -CONH-) ppm., MS (FAB) m/z 733 $(M+1)^+$ (100) 677 (40) 456 (37) 396 (79) 307 (22) 282 (57) 216 (41).

(II) *1-(D-Aminophenylacetyloxy)-1-ethyl [6R-[6α,7β(Z)]]-3-[(acetoxy)methyl]-7-[[(2-amino-4-thiazolyl) (methoxyimino)acetyl]amino]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate (1a and 1b)*

A mixture of compounds 4a and 4b (97.00 mg, 0.13 mmol) was dissolved in CH_2Cl_2 (9 ml) and cooled at 0 ℃. Trifluroacetic acid (3 ml) was added and stirred for 1 h. CH_2Cl_2 and excess trifluroacetic acid were removed in vacuo. The oily residue was chromatographed with reversed phase MPLC (Lobar pre-packed size B column, 310 mm x25 mm, Lichroprep RP-18 40-63 μm) using 0.5

% $TFA_{(aq)}$:CH_3CN = 4:1 (v/v) as the eluent to give 34.00 mg of product 1a (41%) and 28.00 mg (33%) of 1b.

The physicochemical properties of 1a are mp 133℃ decp.; IR (KBr) 1770, 1740, 1680, 1525, 1381, 1200, 1140, 1070, 1040 cm^{-1}; ^1H NMR (400 MHz, D_2O, TFA-d) δ 1.37 (3H, *d*, *J* =*5.3 Hz*, -CHC$\underline{H}_3$), 1.88 (3H, *s*, -$CH_2OCOC\underline{H}_3$), 3.38 (2H, AB*q*, *J* =*18.7 Hz*, 2-H), 3.86 (3H, *s*, -NOC$\underline{H}_3$), 4.42 (2H, AB*q*, *J* =*13.6 Hz*, -C$\underline{H}_2OCOCH_3$), 4.93 (1H, *d*, *J* =*4.5 Hz*, 6-H), 5.10 (1H, *s*, *D*-phenylglycine-α-H), 5.53 (1H, *d*, *J* =*4.5 Hz*, 7-H), 6.89 (1H, *q*, *J* =*5.3 Hz*, -C$\underline{H}CH_3$), 6.91 (1H, *s*, aminothiazolyl 5-H), 7.28 (5H, *m*, ArH) ppm.; DEPT-135 (100 MHz, D_2O+TFA-d): δ 27.65 (-S$\underline{C}H_2$-), 64.46 (-$\underline{C}H_2OCOCH_3$) ppm., HRMS (FAB^+) *m/z* for C_{26} $H_{29}N_6O_9S_2$ ($[M+1]^+$) Calcd. 633.1437, found 633.1461.

The physicochemical properties of 1b are mp 138℃, decp.; IR (KBr) 1790. 1720, 1670, 1530, 1390, 1200, 1140, 1068, 1050, cm^{-1}, ^1H NMR (400 MHz, D_2O, TFA-d): δ 1.28 (3H, d, *J* =*5.4 Hz*, -CHC$\underline{H}_3$), 1.89 (3H, *s*, -$CH_2OCOC\underline{H}_3$), 3.47 (2H, AB*q*, *J* =*18.6 Hz*, 2-H), 3.87 (3H, *s*, -NOC$\underline{H}_3$), 4.74 (2H, AB*q*, *J* =*13.4 Hz*, -C$\underline{H}_2OCOCH_3$), 4.99 (1H, *d*, *J* =*4.6 Hz*, 6-H), 5.12 (1H, *s*, *D*-phenylglycine-α-H), 5.59 (1H, *d*, *J* =*4.6 Hz*, 7-H), 6.92 (1H, *s*, aminothiazolyl 5-H), 6.95 (1H, *q*, *J* =*5.4 Hz*, -C$\underline{H}CH_3$), 7.31 (5H, *m*, ArH) ppm., DEPT-135 (100 MHz, D_2O, TFA-d): δ 27.97 (-S$\underline{C}H_2$-), 64.58 (-$\underline{C}H_2OCOCH_3$) ppm.; HRMS (FAB^+) *m/z* for C_{26} $H_{29}N_6O_9S_2$ ($[M+1]^+$) Calcd. 633.1437, found 633.1440.

III. *Degradation of Compounds 1a and 1b in Phosphate Buffer Solutions*

The test compound, 1a or 1b (10 mg), and benzoic acid (40 mg) as internal standard were dissolved in 10 ml of methanol as the stock solution. The stock solution (200 μg) was dissolved in 9.8 ml of a pH 2.09, 5.47 or 7.39 phosphate buffer solution. The solution was incubated in a water bath at 37℃ and 1 ml of the solution was withdrawn at time intervals from zero to 120 minutes of incubation. The sampled solution (10 μl) was injected into an HPLC column for quantification.

IV. *Degradation of Compounds 1a and 1b in Intestinal Mucosal Suspension*

Mucosal suspension was prepared from the intestine of male Wistar rats according to the method of Hu *et al*[19]. After abdominal incision the intestinal segment between the beginning of the jejunum and the end of the ileum was isolated and everted to let expose the interior. The mucosal layer was washed with normal saline and then scraped with glass microscope slides. The scraping was collected, diluted to the ratio of 1:9 (v/v) with ice cold isotonic sucrose solution, and ultrasonicated for 200 seconds. The suspension was centrifuged at 2500 rpm for 5 minutes and the supernatant suspension was stored in an ice bath before use. Degradation studies were conducted immediately after the mucosal suspension was prepared. A methanolic solution (100 μl) of the test compound (1 mg/ml) was diluted with an isotonic mannitol buffer solution (pH 6.5, 2.4 ml) as the stock solution. This stock solution (100 μl) was mixed with the mucosal suspension (100 μl). Each of the mixtures was incubated in a water bath at 37℃ for a suitable time period from zero to 60 min. The reaction was stopped by adding 0.8 ml of MeOH and the mixture was centrifuged at 14000 rpm for 5 minutes. The supernatant (20 - 100 μl) was subjected to HPLC assay.

V. *Chromatography*

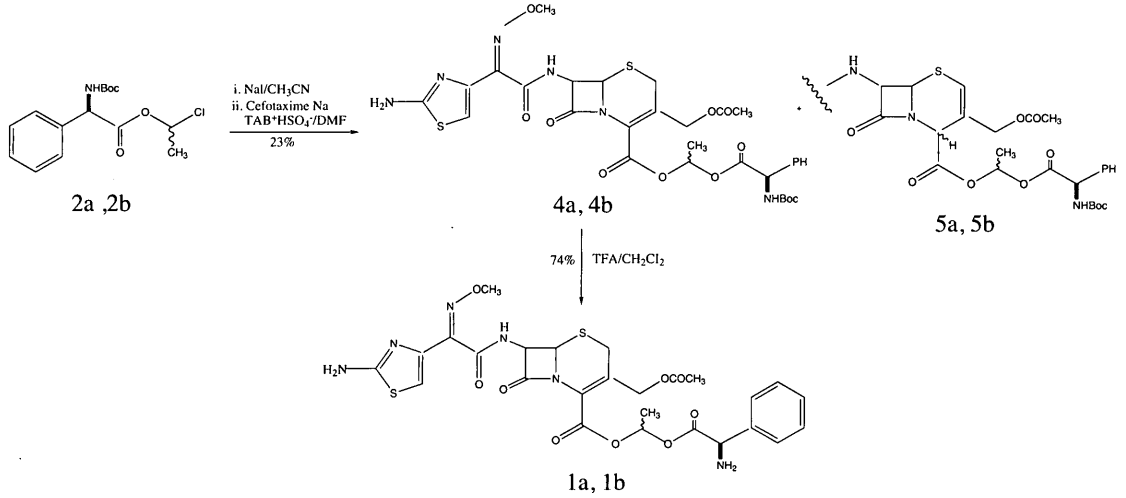
The HPLC system consisted of a Waters 600E pump, a Waters 484 UV/VIS detector set at 254 nm and a Waters 745 Chromatocorder. A solvent system consisting of $CHCl_3$: CH_3CN : MeOH (18 : 5 : 1 v/v, 2.5 ml/min flow rate) was used for the separation of isomeric intermediates 4a, 4b, 5a and 5b in a Nucleosil 5 silica (Vercopack No 4443, 4.6 mm X 250 mm) column. The retention times were 10.3 min and 11.3 min for 4a and 4b respectively and 12.5 min for 5a and 5b. A Lichrospher 100 RP-18 (5 μm, E. Merck) column was used for assaying 1a and 1b. The retention times were 6.4 and 7.5 min for 1a and 1b respectively when eluted with a solvent system consisting of 0.5% $TFA_{(aq)}$: CH_3CN (3 : 1 v/v) at a flow

rate of 1.5 ml/min. Dipeptide L-Gly-L-Phe was assayed in Nova-Pak C-18 (4 μm, 150 mm x 3.9 mm, Waters) using a mixture of 0.1 M phosphate buffer (containing 0.05% dodecyl sulfate sodium, pH 3.4) : CH_3CN (3 : 1 v/v) as the eluent at a flow rate of 0.8 ml/min.

RESULTS AND DISCUSSION

The preparation of 1a and 1b is depicted in Scheme 1. Direct alkylation of cefotaxime sodium with 1-chloroethyl 2-*N*(Boc)-phenylglycine (2a and 2b as diastereomers)[20] failed to give the desired intermediates 4a and 4b. Compounds 2a and 2b were allowed to convert to the iodo analogues 3a and 3b before condensation to cefotaxime sodium. In order to decrease the hardness of the sodium salt of cefotaxime, a variety of phase transfer catalysts, such as 15-crown-5, tetrabutylammonium hydroxide (TBA^+OH^-) and tetrabutylammonium iodide (TBA^+I^-), were added to the reaction mixture. Most of the alkylation reactions, with or with out the addition of phase transfer catalysts, led to four products, as monitored with HPLC. Products 4a and 4b, which appeared in HPLC as peaks A and B respectively (Fig. 1a), were identified as the desired Δ^3 diastereomeric compounds. Products 5a and 5b, appearing as peak C in HPLC, were difficult to separate. These compounds were identified as the undesired Δ^2 isomers of 4a and 4b from an NMR spectrum in which the chemical shifts of 6.64 ppm and 5.02 ppm were interpreted respectively as the C-2 vinyl and the C-4 allylic protons of the cepham ring. Since cefotaxime sodium was fairly stable in the reaction medium in the absence of the alkylating agents 3a and 3b, it is believed that compounds 5a and 5b were generated from 4a and 4b via a $\Delta^3 \rightarrow \Delta^2$ isomerization of the cepham ring [21,22].

That the $\Delta^3 \rightarrow \Delta^2$ conversion might be facilitated under basic condition[22] was demonstrated in this study by the addition of triethylamine (TEA) to the reaction media. As depicted in Fig. 1b, the ratio of peak area C to that of the sum of peak areas A and B increased when TEA was added. The ratio was even higher when TEA was added for a prolonged reaction period (Fig. 1c). In order to prevent the reaction media from being basic, we thus used $TBA^+HSO_4^-$, a quaternary ammonium ion with an acidic counter ion, as the phase transfer catalyst. In comparison to the reaction in the absence of a catalyst (Fig. 1a), this reaction led to a majority of the desired Δ^3 isomers 4a and 4b (Fig. 1d). We thus successfully eliminated the $\Delta^3 \rightarrow \Delta^2$ isomerization commonly reported for the cephalosporin ester antibiotics. Diastereomers 4a and 4b were separated from the side products 5a and 5b by medium pressure liquid chromatography (MPLC). Treatment of the mixture of 4a and 4b with trifluoroacetic acid in methylene chloride afforded the desired products 1a and 1b, which were separated by reverse phase MPLC chro-



Scheme 1

matography.

The stability of compounds 1a and 1b in phosphate buffer solutions at pH 2.09, 5.37 and 7.39 was determined. Samples were assayed for residual compounds with HPLC. The stability profile of compounds 1a (Fig. 2a) and 1b (Fig. 2b) were very similar in pH 2.09, and pH 5.47 buffer solutions. More than 50% of the compounds remained intact after 80 minutes of incubation in both conditions. However, degradation was fairly rapid in pH 7.39 phosphate buffer solution for both compounds. Only 50% of compound 1a was recovered after 8 minutes of incubation and 50% of compound 1b was recovered after 13 minutes of incubation. The degradation products were not identified. However, since Miyauchi has reported that the hydrolysis of Δ^3 cephalosporin esters in alkaline conditions generally proceeds via their Δ^2 isomers[22], we suspected that the instability of compounds 1a and 1b in pH 7.39 phosphate buffer solution was possibly due to their degradation to the Δ^2 isomers via the process of isomerization

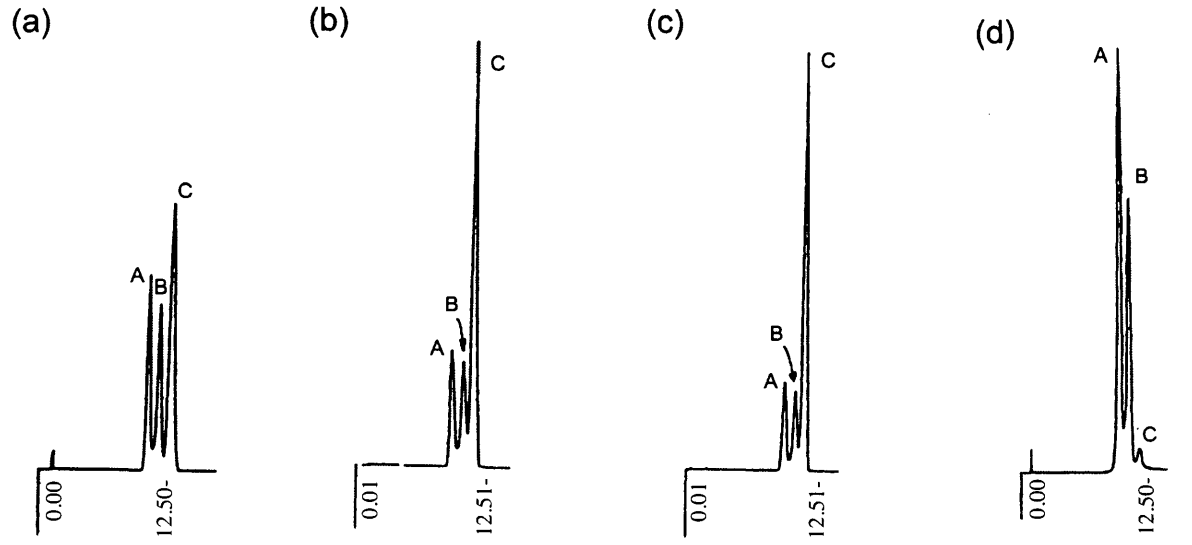


Figure 1. The HPLC chromatographic profile of (a) a reaction of cefotaxime sodium with a mixture of 3a and 3b for 30 minutes of reaction time; (b) similar reaction with TEA added; (c) similar reaction with TEA added for 1 hour of reaction time; and (d) the reaction catalyzed by $TBA^+HSO_4^-$. Peaks A and B were identified respectively as compounds 4a and 4b while peak C was identified as a mixture of compounds 5a and 5b.

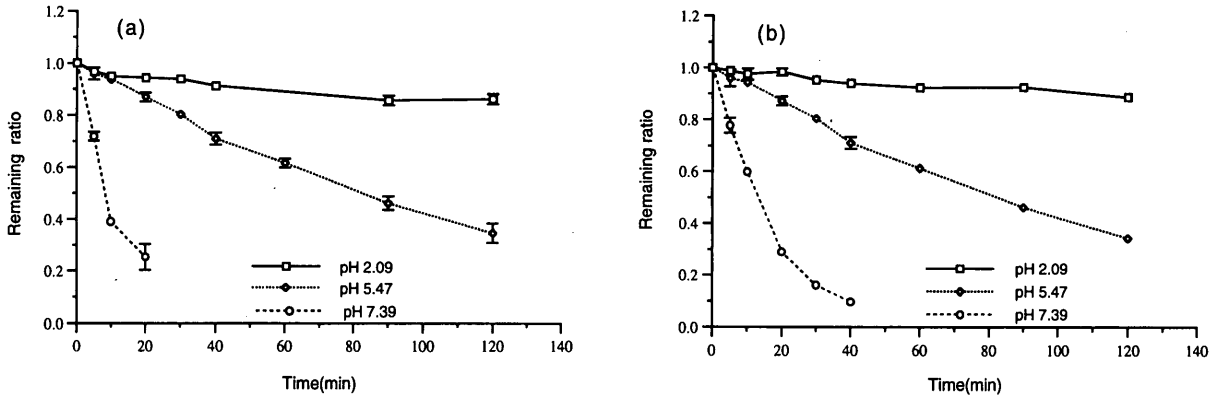


Figure 2. Stability of (a) compound 1a and (b) compound 1b in pH 2.09, 5.47 and 7.39 phosphate buffer solutions at 37 ℃. Each point represents the mean ± S.D. of 3 experiments.

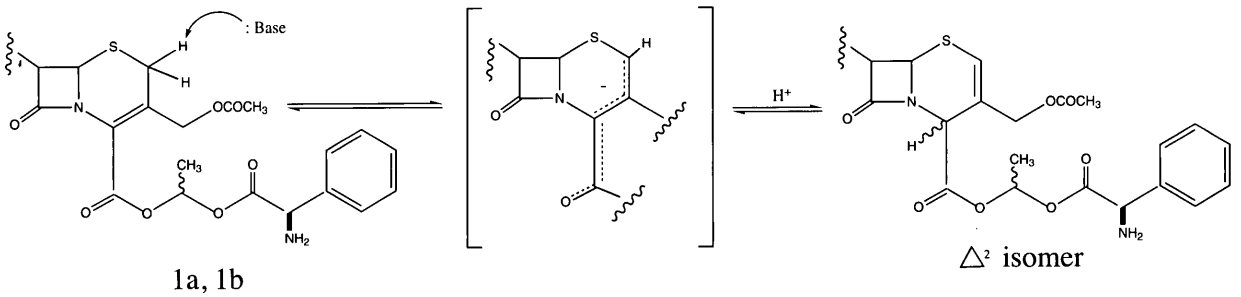


Figure 3. Proposed degradation pathway of compounds 1a and 1b in pH 7.39 phosphate buffer solution.

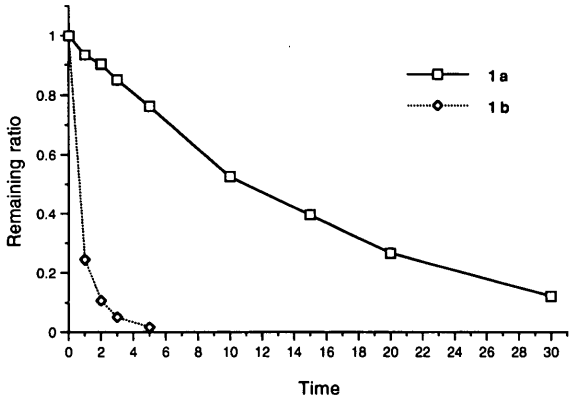


Figure 4. Degradation of compounds 1a and 1b in rat intestinal mucosal suspension. Each point represents the mean ± S.D. of 3 experiments.

(Fig. 3)[23].

Intestinal stability of the prodrugs toward enzymatic degradation was evaluated using a mucosal suspension prepared from rat intestine. The compounds were incubated with the mucosal suspension for a time period from zero to 60 minutes in an isotonic buffer solution at pH 6.5. The enzymatic activity of the mucosal preparation was ensured, as dipeptide L-Gly-L-Phe was degraded rapidly with only 19% of recovery after 2 min of incubation. Both 1a and 1b degraded fairly rapidly with half life of 11 minutes and 1 minute respectively (Fig. 4).

In conclusion, D-phenylglycine was attached at the 4-COOH position of cefotaxime via an ethylidene linkage to form double ester derivatives 1a and 1b. The $\Delta^3 \rightarrow \Delta^2$ isomerization commonly reported for the synthesis of cephalosporin esters was successfully eliminated by the addition of $TBA^+HSO_4^-$ as a phase transfer catalyst in this study. Although the prodrugs 1a and 1b were stable in acidic phosphate buffer solutions, they were degraded fairly rapidly in pH 7.39 phosphate buffer solution. Insufficient stability in rat intestinal mucosal suspension suggested that compounds 1a and 1b are not suitable for formulation as oral prodrugs of cefotaxime.

ACKNOWLEDGMENTS

This study was supported by National Health Research Institute, the Republic of China (grant DD01-86IX-BP-605P, 1997). The supply of cefotaxime sodium from Gentle Pharmaceutical Cooporation Ltd. is appreciated.

REFERENCES

1. Jones, R. N. 1994. The antimicrobial activity of cefotaxime: Comparative multinational hospital isolate surveys covering 15 years. Infection 22 Suppl 3: S152-160.
2. Raddatz, J. K., Ostergaard, B. E. and Rotschafer, J. C. 1995. Therapeutic options for cefotaxime in the management of bacterial infections. Diagn. Microbiol. Infect. Dis. 22: 77-83.
3. Jacobs, R. F., Kaplan, S. L., Schutze, G. E., Dajani, A. S., Leggiadro, R. J., Rim, C. S. and Puri, S. K. 1996. Relationship of MICs to efficacy of cefotaxime in treatment of *Streptococcus pneumoniae* infections. Antimicrob. Agents Chemother. 40: 895-898.
4. Wittmann, D. H. 1995. The role of cefotaxime in the treatment of surgical infections. Diagn. Microbiol. Infect. Dis. 22: 173-182.

5. Niederau, C., Pohlmann, U., Lubke, H. and Thomas, L. 1994. Prophylactic antibiotic treatment in therapeutic or complicated diagnostic ERCP: Results of a randomized controlled clinical study. Gastrointest. Endoc. 40: 533-537.
6. Collignon, P. J. and Bell, J. M. 1996. Drug-resistant *Streptococcus pneumoniae*: The beginning of the end for many antibiotics? Australian Group on Antimicrobial Resistance (AGAR). Med. J. Aust. 164: 64-67.
7. Rawlings, R.D. 1995. Therapeutic exchange of cefotaxime for ceftriaxone: Evaluation, implementation, and subsequent cost savings at a 300-bed community hospital. Diagn. Microbiol. Infect. Dis. 22: 235-237.
8. Gilbert, J. A. and Kamath, P. S. 1995. Spontaneous bacterial peritonitis: An update. Mayo. Clin. Proc. 70: 365-370.
9. Rimola, A., Salmeron, J. M., Clemente, G., Rodrigo, L., Obrador, A., Miranda, M. L., Guarner, C., Planas, R., Sola, R. and Vargas, V. 1995. Two different dosages of cefotaxime in the treatment of spontaneous bacterial peritonitis in cirrhosis: Results of a prospective, randomized, multicenter study. Hepatology 21: 674-679.
10. Fu, K. P., Aswapokee, P., Ho, I., Matthijssen, C. and Neu, H. C. 1979. Pharmacokinetics of cefotaxime. Antimicrob. Agents Chemother. 16: 592-597.
11. Bai, J. P. F. and Amidon, G. L. 1992. Structural specificity of mucosal-cell transport and metabolism of peptide drugs: Implication for oral peptide drug delivery. Pharm. Res. 9: 969-978.
12. Amidon, G. L. and Lee, H. J. 1994. Absorption of peptide and peptidomimetic drugs. Annu. Rev. Pharmacol. Toxicol. 34: 321-341.
13. Okano, T., Inui, K., Maegawa, H., Takano, M. and Hori, R. 1986. H^+-Coupled uphill transport of aminocephalosporins via the dipeptide transport system in rabbit intestinal brush-border membranes. J. Biol. Chem. 261: 14130-14134.
14. Sinko, P. J. and Amidon, G. L. 1989. Characterization of the oral absorption of β-lactam antibiotics ii: Competitive absorption and peptide carrier specificity. J. Pharm. Sci. 78: 723-727.
15. Dantzig, A. H. and Bergin, L. 1990. Uptake of cephalosporin, cephalexin, by a dipeptide transport carrier in the human intestinal cell line, Caco-2. Biochim. Biophys. Acta. 1027: 211-217.
16. Wang, H. P., Lu, H. H., Lee, J. S., Cheng, C. Y., Mah J. R., Hsu, W. L., Yen, C. F., Lin, C. J. and Kuo. H. S. 1996. Intestinal absorption studies on peptido mimetic prodrugs of α-methyidopa. J. Pharm. Pharmacol. 48: 270-276.
17. Wang, H. P., Lee, J. S., Tsai, M. C., Lu, H. H. and Hsu, W. L. 1995. Synthesis, intestinal absorption and pharmacological activities of a novel tripeptide mimetic dopamine prodrug. Bioorg. Med. Chem. Letter 5: 2195-2198.
18. Wang, H. P., Lee, J. S., Tsai, M. C., Lu, H. H., Hu, O. Y. P. and Lo, W. L. 1996. Novel di and tripeptide mimetic compounds for Parkinson's disease. US Patent No. 5,686,423.
19. Hu, M., Subramanian, P., Mosberg, H. I. and Amidon, G. L. 1989. Use of the peptide carrier system to improve the intestinal absorption of l-α-methyldopa : Carrier kinetics, intestinal permeabilities, and in vitro hydrolysis of dipeptide derivatives of l-α-methyldopa. Pharm. Res. 6: 66-70.
20. Lee, J. S., Sun, C. H. and Wang, H. P. 1997. Preparation of D-phenylglycinyl derivatives of cefuroxime as double ester prodrugs. Chin. Pharm. J. 49: 195-205.
21. Hussain, A. A., Saab, A. N. and Dittet, L. W. 1988. Isomerization of cephalosporin ester: Implication for the prodrug ester approach to enhancing the oral bioavailability of cephalosporin. J. Pharm. Sci. 77: 906-907.
22. Miyauchi, M., Sasahara, K., Fujimoto, K. and Kawamoto, I. 1989. Studies on oral active cephalosporin ester. II. Chemical stability of pivaloyloxymethyl esters in phosphate buffer solution. Chem. Pharm. Bull. 37: 2369-2374.
23. Stella, V. J., Richter, W. F. and Chong Y. H. 1990. On the mechanism of isomerization of

cephalosporin ester. J. Pharm. Sci. 79: 185-187.

含D-Phenylglycine之Cefotaxime雙酯先驅藥的合成研究

宋啟華　王惠珀*

臺大醫學院藥學研究所

摘　要

本研究以研發cefotaxime的口服先驅藥爲目標。我們將cefotaxime第四位置之羧基與D-phenylglycine之羧基以亞乙基作爲橋鍵形成雙酯先驅藥1a及1b，期使該先驅藥透過D-phenylglycine與腸膜上雙胜肽載體輸遞系統的親合力而穿透腸壁吸收。合成先驅藥1a及1b的方法係將1-iodoethyl2-N(Boc)-phenylglycine (3a及3b) 與cefotaxime sodium縮合形成中間體4a及4b，再去除Boc保護基形成目標產物1a及1b。縮合反應中出現cepham環$\Delta^3 \rightarrow \Delta^2$異構化反應，產生$\Delta^2$異構物5a及5b。我們使用具有酸性抗衡離子之四級胺鹽tetrabutylammonium hydrogen sulfate作爲縮合反應催化劑，可成功防止異構化現象之發生。先驅藥1a及1b在pH2.09及pH5.47之磷酸緩衝溶液中安定性甚佳，然而在pH7.39緩衝溶液中則快速分解，其中1a之半衰期爲8分鐘，1b爲13分鐘。這二個先驅藥在離體老鼠小腸黏膜培養液中的安定性亦不理想，其半衰期分別爲11分鐘及1分鐘。分解速率過速，致化合物1a及1b無法成爲理想之cefotaxime先驅藥。

關鍵詞：cefotaxime雙酯先驅藥，合成，安定性。