SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF 7-[2-(2-AMINOOXAZOL-4-YL)-(Z)-2-ALKOXYIMINOACETAMIDO]-CEPHALOSPORIN ANTIBIOTICS

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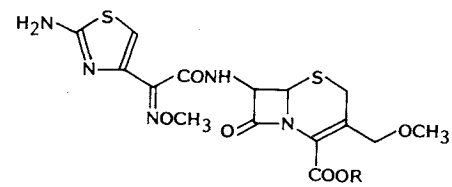
In recent years, some cephalosporins having an aminothiazole-oxime moiety at the C-7 position of the cephem nucleus have been developed for oral use[1~3].

In a previous paper[3], we reported on the synthesis and the biological activity of 3-methoxymethyl cephalosporin derivatives, one of which, cefpodoxime proxetil (Fig. 1), has been successfully developed as a prodrug for oral use. Our further elaboration for developing orally active cephalosporins has been made in the direction of chemical modification of the C-7 acyl substituent of the 3-methoxymethyl cephalosporin derivatives.

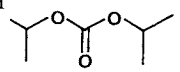
7-[2-(2-Aminooxazol-4-yl)-(Z)-2-alkoxyimino-acetamido]-3-methoxymethyl cephalosporin derivatives (**4** and **5**) were prepared in a similar manner to that described in previous papers[3,4] as illustrated in the following scheme.

The antibacterial activity of the 7-aminooxazolyl derivatives (**4a**~**4e**) is shown in Table 1. These compounds showed fairly good potency against the tested organisms especially against Gram-positive strains. Among them, methoxime (**4a**) and 2-

Fig. 1. Structure of cefpodoxime and cefpodoxime proxetil.



Cefpodoxime R=H
Cefpodoxime proxetil R=



Scheme 1.

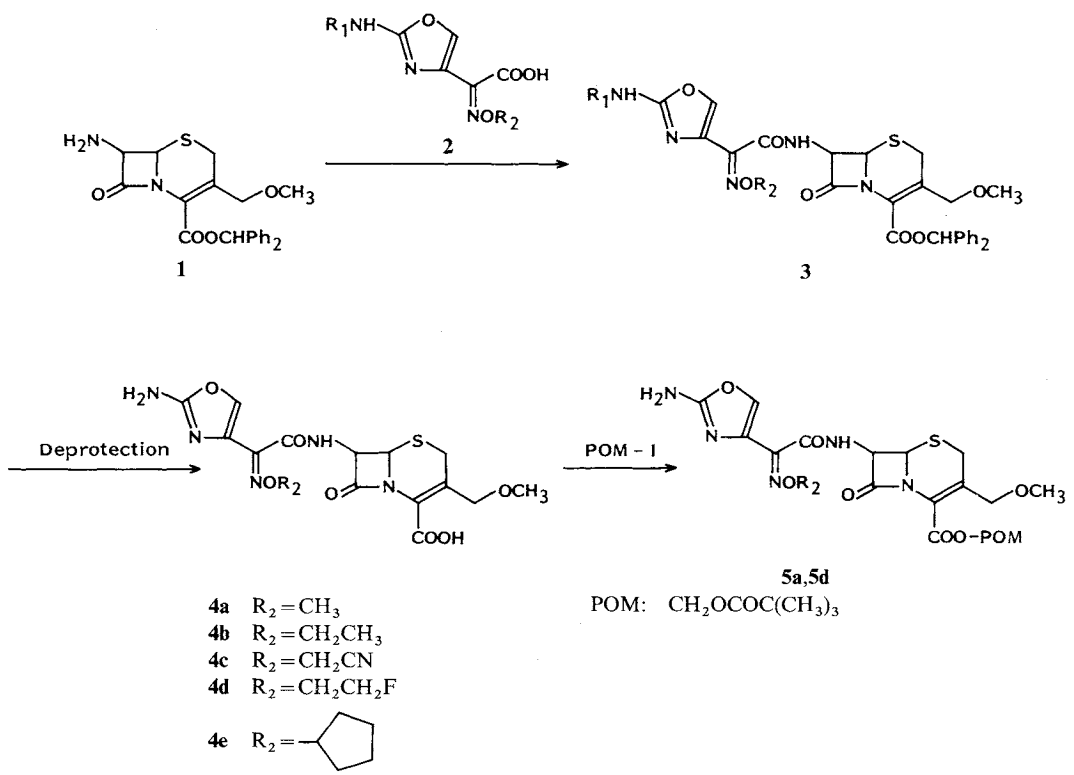


Table 1. Antibacterial activity (MIC, μg/ml)[a] of 7-aminooxazolyl derivatives (**4a**~**4e**).

Organism	**4a**	**4b**	**4c**	**4d**	**4e**	CPDX[b]
Staphylococcus aureus 209P JC-1	0.4	0.2	0.8	0.4	0.1	0.8
S. aureus 56[c]	0.8	0.8	1.5	0.8	0.4	0.8
Escherichia coli NIHJ JC-2	1.5	6.2	12.5	1.5	12.5	0.4
E. coli 609[c]	3.1	6.2	25	3.1	12.5	0.4
Klebsiella pneumoniae 806	0.4	1.5	3.1	0.4	12.5	0.1
Proteus vulgaris 1420	0.4	0.1	0.4	0.1	$\leqq$0.01	$\leqq$0.01

[a] Agar dilution method: Nutrient agar; 10^7 cfu/ml.
[b] Cefpodoxime.
[c] β-Lactamase producing strains.

fluoroethoxime (**4d**) derivatives exhibited excellent activity, however, the potency against Gram-negative organisms was slightly inferior to that of cefpodoxime. The subsequent introduction of an electron-withdrawing (**4c**) or a lipophilic (**4b** and **4e**) moiety in place of the methyl group on the oxime substituent did not lead to a significant improvement in activity.

Although the acid derivatives (**4**) exhibited potent antibacterial activity, they showed poor urinary recovery after oral administration to mice. Consequently, the acids were converted to orally active pivaloyloxymethyl (POM) esters[2,5,6] (**5**). The POM ester derivatives **5a** (R_2=CH_3) and **5d** (R_2=CH_2CH_2F) showed remarkably improved urinary recoveries of 67% and 45%, respectively.

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