STRUCTURE-ACTIVITY RELATIONSHIPS OF SOME 6α-FORMAMIDO PENICILLINS

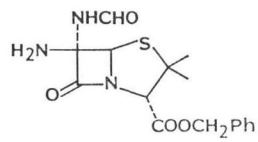
Sir:

During a programme of chemical synthesis in these laboratories designed to discover novel 6α(7α)-substituents which would enhance the antibacterial properties of penicillins and cephalosporins, we identified the 6α(7α)-formamido substituent as a promising candidate. We have previously outlined the synthesis of such β-lactams[1,2]. Other workers have described the isolation of a number of 7α-formamido cephalosporins[3~8] and two 3α-formamido nocardicin analogues[9,10] from bacterial culture filtrates. We now report the antibacterial properties of a number of 6α-formamido penicillins.

These compounds were most directly available by the acylation of benzyl 6β-amino-6α-formamidopenicillanate (**1**)[2] with an appropriately activated side chain acid derivative, followed by hydrogenolysis to afford the free penicillin, generally isolated as its sodium salt (method A, Table 1). Many of the derivatives described were of the α-acylamino or α-acylureido type with side chains based on a substituted phenylglycine. They were often conveniently prepared by acylation of **1** with a protected phenylglycine to give **2**, followed by hydrogenolysis to give the α-aminopenicillin (**3**) and final acylation to give the desired compound (method B, Table 1). Full chemical details will be published subsequently.

The antibacterial activities of the 6α-formamido penicillins are shown in Table 1. It will be seen that these compounds were highly active against a number of Gram-negative bacteria, including β-lactamase producing strains, but showed little or no activity against the Oxford strain of *Staphylococcus aureus*, which is highly-sensitive to benzylpenicillin. In the acylureido series (**4a**~**4d**) it will be seen that the introduction of one hydroxyl group into the benzene ring (compound **4b**) gave some improvement in activity over the unsubstituted **4a**, while the 3,4-dihydroxy compound (**4c**), described previously as BRL 36650[11], was by far the most active. This compound showed potent activity against members of the family Enterobacteriaceae including strains of *Escherichia coli* and also against *Pseudomonas aeruginosa*. The 2-thienyl compound (**4d**) was similar in activity to the unsubstituted phenyl compound (**4a**). Other derivatives of the acylureido type are compounds **5a**~**5d**: they also exhibited good activity against Gram-negative bacteria, the pyrimidinyl analogue (**5a**) being as active as **4b**, though loss of activity against *P. aeruginosa* was noted in **5b**, **5c** and the non-heterocyclic analogue (**5d**). In the acylamino series, compound **6a** was almost equi-active with **5b** and **5c**; here also, the 3,4-dihydroxyphenyl substituent, as in **6b**, noticeably improved the activity against *E. coli* and *P. aeruginosa* strains. Other 6α-formamido penicillins bearing phenoxyacetamido, α-aminobenzyl, and 3-(α-carboxy)-thienyl-methyl side-chains showed poor antibacterial activity.

In order to define more precisely the role of the 6α-formamido substituent, the activities of the 6-unsubstituted compounds (**7a** and **7b**) have been added to Table 1. It will be seen for both pairs **4a** and **7a**, **4c** and **7b** the intrinsic activities are very similar against the non-β-lactamase producing strains of the Gram-negative organisms *E. coli* and *P. aeruginosa*. The difference made by the 6α-formamido substituent lies primarily in stability to β-lactamases. This may be seen by comparing the MIC values against *E. coli* JT4 and *P. aeruginosa* Dalgleish, which produce plasmid-mediated TEM-1 and PSE-4 β-lactamases respectively, against which the unsubstituted penicillins (**7a** and **7b**) exhibit little or no antibacterial activity. Compared to 6α-methoxy penicillins of the acylamino and acylureido series[12], where the 6-substituent provides β-lactamase stability at the expense of some activity,



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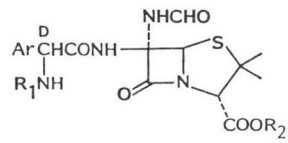


2 $R_1 = COOCH_2C_6H_4p\text{-}NO_2$, $R_2 = CH_2Ph$

3 $R_1 = R_2 = H$

Table 1. Minimum inhibitory concentrations[a] (μg/ml) of 6α-formamido penicillins and two 6α-H penicillins.

Organism	Derivative (Method of preparation)[b]											
	4a (A)	**4b** (A)	**4c** (A)	**4d** (B)	**5a** (B)	**5b** (B)	**5c** (B)	**5d** (B)	**6a** (B)	**6b** (B)	**7a** (−)	**7b** (−)
Escherichia coli ESS[c]	0.12	≤0.02	≤0.06	≤0.02	0.25	≤0.02	≤0.02	≤0.02	0.25	0.12	≤0.06	≤0.03
E. coli JT4[d]	0.5	2.5	≤0.06	0.5	1.0	1.0	—	5.0	5.0	0.5	>100	>100
E. coli JT425[e]	1.0	1.0	0.5	0.5	1.0	1.0	2.5	2.5	2.5	1.0	16	16
E. coli NCTC 10418	0.25	0.5	≤0.06	0.5	1.0	1.0	0.5	2.5	2.5	0.12	0.5	≤0.03
Pseudomonas aeruginosa NCTC 10662	16	1.0	0.5	25	5.0	>100	50	>100	100	2.0	4.0	0.2
P. aeruginosa Dalgleish[d]	16	5.0	0.5	25	2.5	100	25	>100	50	2.0	>100	>100
Serratia marcescens US32	1.0	0.5	0.12	0.5	2.5	1.0	1.0	1.0	2.5	8.0	1.0	1.0
Klebsiella aerogenes A	2.0	1.0	≤0.06	0.5	2.5	0.5	1.0	5.0	2.5	1.0	2.0	1.0
Enterobacter cloacae N1	1.0	0.5	0.12	0.5	0.5	1.0	2.5	2.5	2.5	8.0	1.0	0.5
Proteus mirabilis 889	0.12	0.1	0.12	0.1	0.5	0.1	0.25	1.0	1.0	2.0	>100	>100
Staphylococcus aureus Oxford	>100	>100	>100	>100	100	>100	>100	50	>100	>100	0.5	4.0
Streptococcus pyogenes CN10	0.5	0.5	2.0	1.0	1.0	25	0.1	0.25	5.0	8.0	0.06	0.02

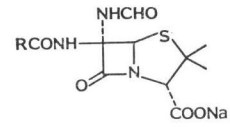
[a] MIC values were determined by serial dilution in Blood Agar Base (Oxoid) against an inoculum of 1×10^6 cfu.

[b] Methods of preparation A, B: See text.

[c] Cell wall deficient mutant.

[d] Plasmid-mediated β-lactamase producing strain.

[e] Non-plasmid-mediated β-lactamase producing strain.



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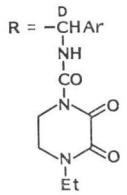

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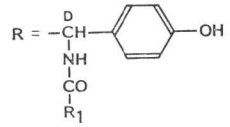

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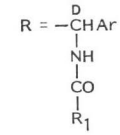

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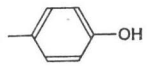
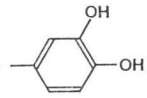
b Ar = 

c Ar = 

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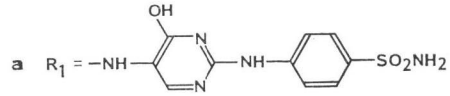
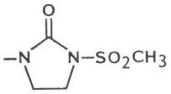
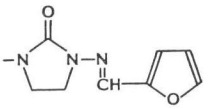
a R_1 = 

b R_1 = 

c R_1 = 

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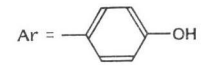
a Ar = 

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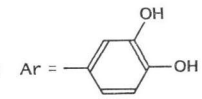
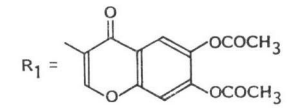
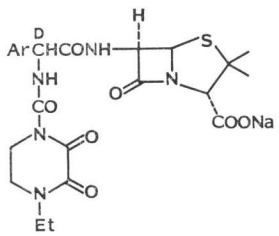
b Ar = 

R_1 = 



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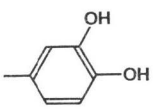
b Ar = 

the derivatives **4a**→**6b** described here exhibit β-lactamase stability without compromising intrinsic activity. This may reflect different penicillin binding protein affinities for the two 6-substituted penicillin classes.

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