PREPARATION AND ANTIBACTERIAL ACTIVITY OF A SERIES OF 6α-METHOXY PYRIMIDINYLUREIDOPENICILLINS

Sir:

Recent publications[1,2] have again highlighted the potent broad-spectrum antibacterial activity of sodium 6*R*-[(*R*)-2-[3-[2-(4-aminosulfonyl)-anilino-4-hydroxy-5-pyrimidinyl]ureido]-2-(4-hydroxyphenyl)acetamido]penicillanate (**1**). One weakness of this class of compounds is their lack of stability to bacterial β-lactamases. Earlier work in these laboratories[3] demonstrated how the introduction of a 6α-methoxy group into penicillins gave good stability to these enzymes, although in the case of acylamino penicillins (*e.g.* piperacillin) this was usually accompanied by a dramatic loss in overall activity. We wish to report the synthesis and antibacterial activity of a series of 6α-methoxy analogues of **1**.

The protected D or DL amino acids[4] (**2a**~g; X=NO_2, **h**; X=H) were coupled to benzyl 6β-amino-6α-methylthiopenicillanate[5] (**3**) using either acid chloride (**2a**~g) or *N*,*N*′-dicyclohexylcarbodiimide (**2h**) activation (Scheme 1). For the 2-thienyl examples (**2f** and **g**) the DL amino acid derivative was coupled and the diastereoisomers separated by chromatography. The 6α-methylthio group was displaced by methoxy using mercuric acetate in MeOH, followed by hydrogenolysis to give the amino penicillins (**4a**~**h**). Reaction with the *N*-carbonylchloride (**5**) gave, after sodium salt formation, the required pyrimidinylureido 6α-methoxypenicillins (**6a**~**h**).

The *in vitro* activity of **1** and the 6α-methoxy derivatives is shown in Table 1. The 6α-methoxy analogue (**6a**) of **1** showed excellent stability to various β-lactamases, including the R-TEM enzyme as produced by *Escherichia coli* JT4. The MIC values for β-lactamase producing strains were similar to those for non-producing strains. Intrinsic activity was reduced particularly against Gram-positive organisms, and, in most cases, against *Pseudomonas aeruginosa*. Variation of the substituent R led to a series of 6α-methoxy penicillins (**6b**~**h**), all stable to β-lactamases, but with a markedly

Scheme 1.

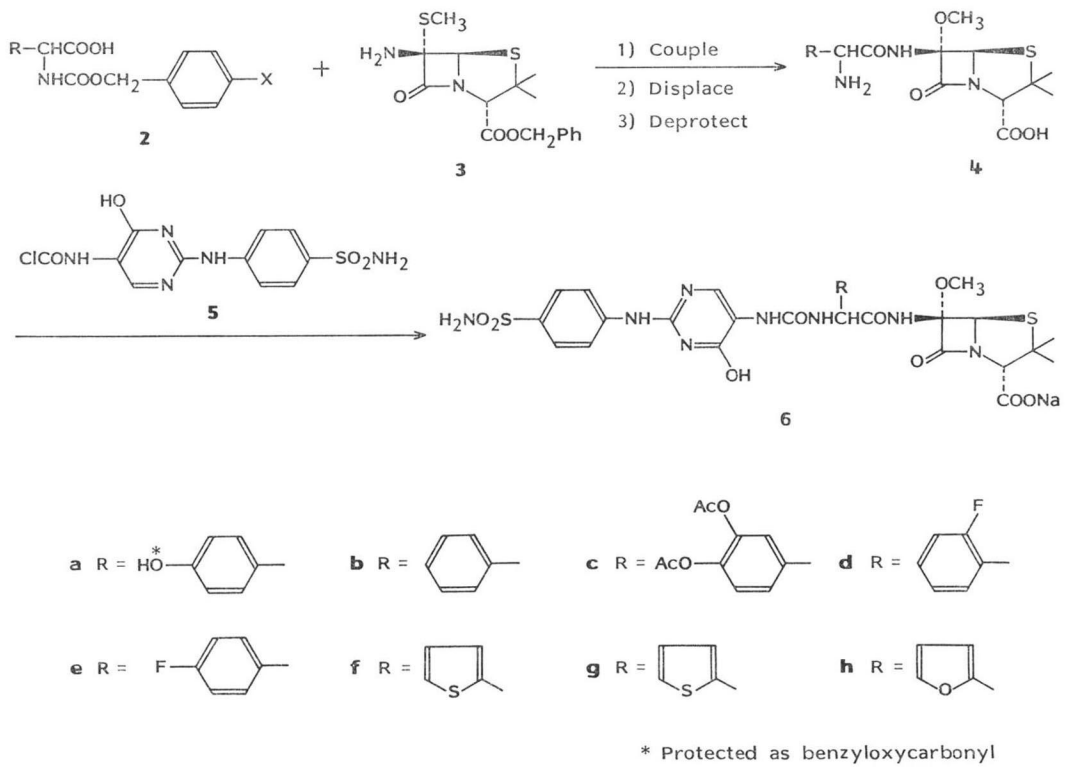
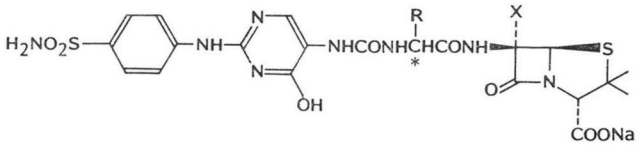


Table 1. Antibacterial activity of **1** and its 6α-methoxy analogues (MIC (μg/ml))[a].



	*	**1**	**6a**	**6b**	**6c**	**6d**	**6e**	**6f**	**6g**	**6h**
		D	D	D	DL	DL	DL	D	L	DL
	R	HO-	HO-		AcO, AcO-	F	F-	S	S	O
	X	H	OCH_3	OCH_3	OCH_3	OCH_3	OCH_3	OCH_3	OCH_3	OCH_3
Escherichia coli NCTC 10418		0.25	1.25	2.5	$\leq$0.06	0.5	10	1	2.5	0.5
E. coli JT4[b]		>100	0.5	2.5	$\leq$0.06	1.25	10	2.5	2.5	1.25
E. coli JT425[c]		10	2.5	2.5	1.25	1.25	25	1	2.5	10
Pseudomonas aeruginosa NCTC 10662		2.5	25	50	1.25	10	>100	10	50	25
Serratia marcescens US32		2.5	5	10	2.5	2.5	25	2.5	10	5
Klebsiella pneumoniae A		10	0.2	2.5	$\leq$0.06	0.25	10	0.2	1	0.12
Enterobacter cloacae N1		0.5	1.25	2.5	2.5	1.25	25	0.5	2.5	1
Proteus mirabilis C977		0.25	1.25	2.5	2.5	1.25	10	1	2.5	2.5
P. mirabilis 889[c]		>100	1.25	1	2.5	0.5	10	0.5	2.5	1
Staphylococcus aureus Oxford		1	50	10	>100	10	50	10	25	25
S. aureus Russell[b]		>100	50	10	>100	25	50	10	25	50
Enterococcus faecalis I		2.5	>100	>100	>100	>100	>100	>100	>100	>100

[a] Determined by serial dilution in nutrient agar containing 5% defibrinated horse blood, inoculum 0.001 ml of an overnight broth culture (approximately 10^6 cfu).

[b] β-Lactamase producing strain (plasmid-mediated).

[c] β-Lactamase producing strain (non-plasmid-mediated).

different antibacterial spectrum.

Thus, the excellent Gram-negative activity of **6c**, including *P. aeruginosa* is offset by the total loss of Gram-positive activity. In contrast **6f**, whilst showing a slight loss of activity against Gram-negative organisms retains, in common with **6b**, a moderate level of potency against *Staphylococcus aureus*.

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DESMOND J. BEST*
GEORGE BURTON
FRANK P. HARRINGTON
JOHN LOWTHER

Beecham Pharmaceuticals,
Research Division,
Brockham Park,
Betchworth,
Surrey, RH3 7AJ,
United Kingdom

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