SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF NOVEL PYRAZOLINONE PENICILLINS

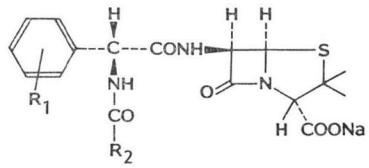
Sir:

Certain penicillins of general structure (**1**), containing an arylglycine side chain further acylated at the α-nitrogen, possess potent, broad spectrum antibacterial activity. Piperacillin[1] (**2**) is established as a leading commercial example of this type.

We report the synthesis and *in vitro* antibacterial properties of a novel series of acylated pyrazolinone penicillins[2] (**3**$\sim$**5**). The ampicillin derivatives (**3a**$\sim$**w**) were synthesised from the appropriate acids (**6a**$\sim$**w**) as follows. The relevant acid chloride (**7a**$\sim$**w**) was first prepared (usually with thionyl chloride - triethylamine) and, *in situ*, was protected as its silyloxy pyrazole derivative (**9a**$\sim$**w**) (trimethylsilyl chloride - triethylamine). This was then treated with ampicillin and triethylamine, aqueous workup liberating the desired penicillins (**3a**$\sim$**w**). The *p*-hydroxyl analogue (**4**) was prepared in a similar manner from amoxycillin and acid (**6h**). The aminophenyl pyrazolinone examples (**3x, y**) were prepared by hydrogenation of the corresponding nitro-analogues (**3b, c**).

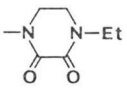
Per-trimethylsilylation of D-dihydroxyphenylglycine (**10**) followed by coupling with pyrazole (**9h**), prepared as described above, gave the side-chain acid (**11**) which was subsequently triacetylated and coupled *via* its methoxycarbonyl mixed anhydride to the benzyl ester of 6-aminopenicillanic acid. Hydrogenation gave the penicillin (**5**).

The pyrazolinone acids (**6a**$\sim$**w**) were obtained from the pyrazolinone esters[2,3] (**8a**$\sim$**f**) as follows. *p*-Methoxy ester (**8f**) could be converted (boron tribromide) to its *p*-hydroxyl analogue (**8g**). Saponification of esters (**8a**$\sim$**g**) directly afforded acids (**6a**$\sim$**g**). The nitro esters (**8b, c**)

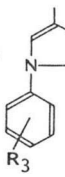


1

2 R_1 = H, R_2 =

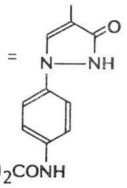


3 R_1 = H, R_2 =

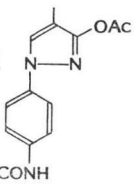


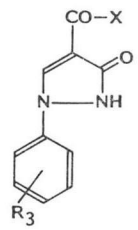
, R_3 = see Table 1.

4 R_1 = *p*-OH, R_2 =

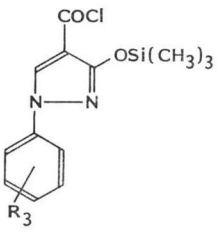


5 R_1 = *m, p*-di-OAc, R_2 =

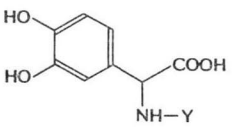




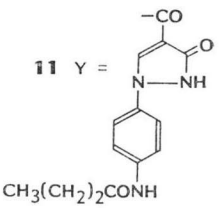
6 X = OH, R_3 = see Table 1.
7 X = Cl, R_3 = see Table 1.
8 X = OEt, R_3 = see Table 1.



9 R_3 = see Table 1.

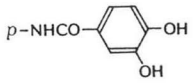
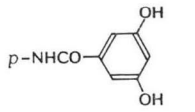


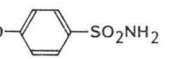
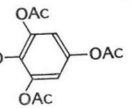
10 Y = H



11 Y =

Table 1. The antibacterial activities *in vitro* of **3a**~**y**, **4**, **5** and piperacillin (**2**) (MIC (μg/ml))[a].

	R_3	Pe[b]	*Ec*N	*Ec*J	*Pa*N	*Pa*D	*Sm*	*Kp*	*Ecl*	*Pm*	*Mm*	*Pr*	*Sa*O	*Sa*R[c]	*Ef*	*Sp*
a	H	**3a**	1.0	>128	2.0	>128	4.0	8.0	1.0	0.25	2.0	1.0	0.25	32	8.0	0.12
b	*p*-NO_2	**3b**	2.5	>100	25	>100	10	10	5.0	2.5	25	5.0	2.5	100	25	0.5
c	*m*-NO_2	**3c**	1.0	>128	8.0	>128	8.0	8.0	2.0	2.0	2.0	2.0	0.25	32	8.0	<0.06
d	*p*-Br	**3d**	1.0	>64	8.0	>64	2.0	8.0	2.0	1.0	1.0	2.0	0.5	16	4.0	0.12
e	*p*-SO_2Me	**3e**	0.5	>128	4.0	>128	4.0	32	0.25	0.25	0.5	0.25	2.0	32	16	0.12
f	*p*-OMe	**3f**	1.0	>128	4.0	>128	2.0	8.0	1.0	0.5	1.0	0.5	0.5	64	4.0	0.12
g	*p*-OH	**3g**	2.0	>128	4.0	>128	2.0	8.0	0.5	0.25	0.5	0.5	0.5	32	8.0	0.12
h	*p*-$NHCO(CH_2)_2CH_3$	**3h**	0.5	>128	4.0	>128	1.0	2.0	<0.06	<0.06	0.12	<0.06	0.5	32	4.0	<0.06
i	*p*-$NHCOCH_2CH_3$	**3i**	0.5	>128	2.0	>128	2.0	8.0	<0.06	0.12	0.12	<0.06	1.0	32	16	<0.06
j	*p*-NHCOPh	**3j**	0.25	>128	4.0	>128	0.25	2.0	0.25	0.25	0.25	0.12	0.5	128	4.0	<0.06
k	*p*-$NHCO_2CH_2CH_3$	**3k**	1.0	>128	4.0	>128	2.0	8.0	0.25	0.25	0.25	0.12	0.5	64	8.0	—
l	*p*-$NHCO_2CH_3$	**3l**	1.0	>128	4.0	>128	2.0	16	0.25	0.25	0.25	0.25	1.0	128	4.0	<0.06
m	*p*-$NHCOCH_2Ph$	**3m**	0.5	>128	4.0	>128	2.0	32	0.25	0.25	0.5	0.25	1.0	128	8.0	<0.06
n		**3n**	0.06	>128	>128	>128	0.5	2.0	0.5	0.5	0.5	0.25	2.0	128	8.0	—
o		**3o**	0.25	>128	4.0	>128	1.0	4.0	0.5	0.5	1.0	0.5	0.5	128	4.0	<0.06

p	*p*-NHCOCH(CH$_3$)NHCOCH$_3$	**3p**	0.5	>128	4.0	>128	8.0	32	—	0.25	0.25	0.25	2.0	>128	16	<0.06
q	*p*-NHCONHCH$_3$	**3q**	1.0	>128	4.0	>128	4.0	16	0.25	0.25	8.0	0.25	2.0	>128	16	—
r	*p*-NHCOCH$_3$	**3r**	2.5	>100	5.0	>100	5.0	25	0.5	0.5	1.0	0.5	1.0	25	25	0.25
s	*p*-NHCHO	**3s**	1.0	>128	8.0	>128	32	32	0.5	0.5	1.0	0.5	2.0	128	16	0.25
t	*m*-NHCO$_2$Me	**3t**	2.0	>128	4.0	>128	4.0	16	2.0	2.0	8.0	2.0	1.0	—	8.0	<0.06
u		**3u**	1.0	>128	8.0	>128	8.0	64	2.0	0.5	8.0	4.0	0.5	>128	16	0.12
v	*m*-NHCO(CH$_2$)$_2$CH$_3$	**3v**	1.0	>128	4.0	>128	8.0	16	2.0	2.0	32	4.0	2.0	—	16	0.06
w		**3w**	2.0	>128	64	>128	128	64	16	16	16	16	4.0	64	64	0.5
x	*p*-NH$_2$	**3x**	4.0	>128	4.0	>128	16	32	1.0	1.0	2.0	0.5	2.0	>128	16	0.12
y	*m*-NH$_2$	**3y**	2.0	>128	8.0	>128	16	32	2.0	2.0	32	4.0	4.0	64	64	0.25
		4	0.5	>128	2.0	>128	1.0	8.0	<0.06	0.12	0.12	<0.06	1.0	>128	16	<0.06
		5	<0.06	>128	0.12	>128	1.0	2.0	0.25	0.25	0.12	0.25	8.0	128	32	0.5
		2	0.5	>128	4.0	>128	1.0	2.0	1.0	0.25	0.5	0.5	0.5	>128	2.0	0.06

[a] Determined by serial dilution in an appropriate agar medium. Plates inoculated with 1 μl of an undiluted overnight broth culture (approximately 10^6 cfu) and incubated at 37°C for 18 hours.

[b] Pe; Penicillin, *Ec*N; *Escherichia coli* NCTC 10418, *Ec*J; *E. coli* JT 4 (R-TEM), *Pa*N; *Pseudomonas aeruginosa* NCTC 10662, *Pa*D; *P. aeruginosa* Dalgleish (PSE-4), *Sm*; *Serratia marcescens* US 32, *Kp*; *Klebsiella pneumoniae* A, *Ecl*; *Enterobacter cloacae* N1, *Pm*; *Proteus mirabilis* C977, *Mm*; *Morganella morganii*, *Pr*; *Providencia rettgeri*, *Sa*O; *Staphylococcus aureus* Oxford, *Sa*R; *S. aureus* Russell, *Ef*; *Enterococcus faecalis* I, *Sp*; *Streptococcus pyogenes* CN10.

[c] β-Lactamase-producing strain.

were also hydrogenated (H_2/Pd-C) and hydrolysed to the amino acids (**6x, y**). These were in turn per-trimethylsilylated and thus selectively *N*-acylated to the desired pyrazolinones (**6h ~ w**) using appropriate acylating agents (acid chlorides, *etc.*).

The biological activities of the pyrazolinone penicillins are shown in Table 1. Ampicillin derivatives (**3a ~ g, x, y**), which possessed R_3-substituents other than acylamino, showed broad-spectrum activity but overall were less active than piperacillin (**2**). However the potency of certain ampicillin derivatives with an acylamino R_3-group (**3h ~ w**) was greater than that of other analogues. This increase in activity was generally seen where a hydrophobic *p*-R_3-group was chosen, most notably with the *p*-butyramido analogue (**3h**). This compound was similar in activity to piperacillin against most organisms and more active against *Enterobacter cloacae* and *Proteus* species. The analogous amoxycillin derivative (**4**) showed similar activity against Gram-negative bacteria but was slightly less active than **3h** against Gram-positive cocci; this pattern was also noted with other amoxycillin analogues not listed in the Table 1. The diacetoxyphenylglycine derived *p*-butyramido analogue (**5**) showed markedly improved activity against piperacillin-sensitive strains of *Pseudomonas aeruginosa* and *Escherichia coli*, but was less effective against Gram-positive bacteria.

Like piperacillin (**2**), the pyrazolinone penicillins showed little or no activity against strains producing plasmid-mediated β-lactamases, *e.g. E. coli* JT4 (R-TEM), *P. aeruginosa* Dalgleish (PSE-4) or *Staphylococcus aureus* Russell.

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2) COOK, R. T. & A. W. TAYLOR (Beecham Group): β-Lactam antibacterial agents and compositions containing them. U.S. 4,537,886, 1985
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