STRUCTURE-ACTIVITY RELATIONSHIPS OF SOME ARYLGLYCINE ANALOGUES AND CATECHOL ISOSTERES OF BRL 36650, A 6α-FORMAMIDO PENICILLIN

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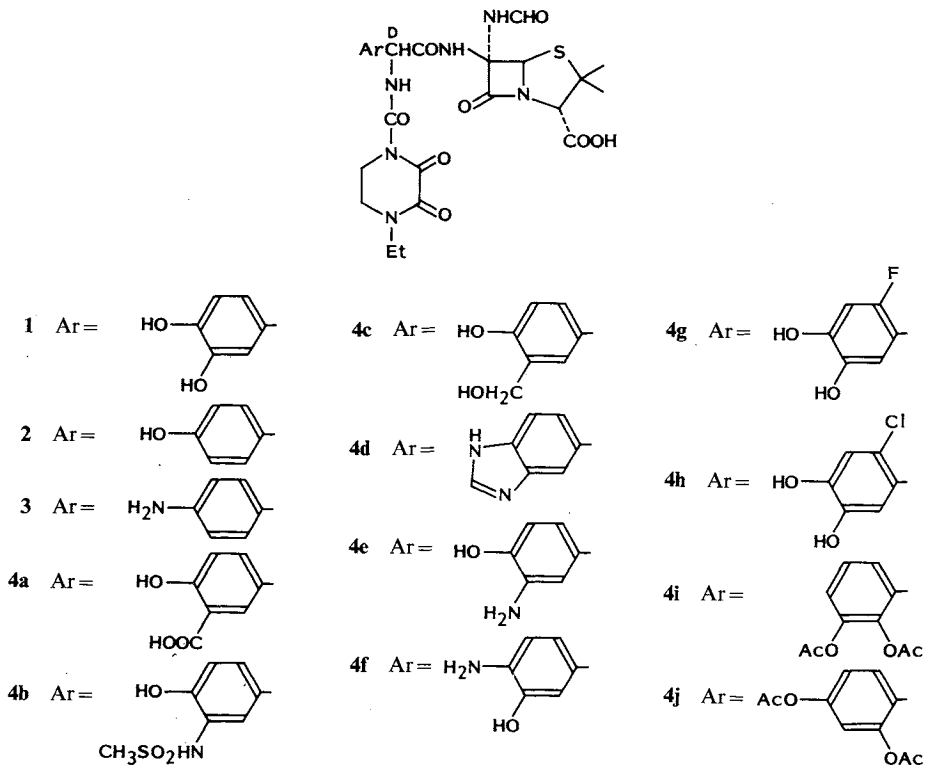
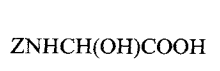
Earlier reports from these laboratories outlined the preparation[1] and biological properties[2,3] of 6α-formamido penicillins. The catecholic acylureido derivative BRL 36650 (**1**) was the most potent, especially against *Pseudomonas aeruginosa* strains. We now report on analogues of **1** which either retain a catechol or dihydroxyphenyl unit or contain various catechol isosteres.

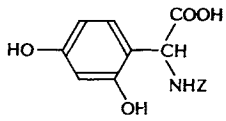
The general concept of isosteric modification in drug design has been reviewed[4]. Catechol isosteres are meant to prevent enzymic methylation, in particular by catechol *O*-methyl transferase into less active monomethyl ethers as reported for other β-lactams[5]. Frequently the *para*-hydroxy group has been retained and the *meta*-hydroxy replaced with a group bearing a relatively acidic proton[6,7] such as carboxy (**4a**), methanesulfonamido (**4b**), or hydroxymethyl (**4c**). Heterocycles such as pyridones and benzimidazoles (**4d**)[4] have also been employed. As the 4-hydroxy (**2**)[3] and 4-amino (**3**) compounds had similar activity, amino-hydroxy analogues (**4e** and **4f**) were included in the programme. Other analogues featured two further-substituted catechols (**4g** and **4h**), a protected 2,3-catechol (**4i**) and a protected 2,4-dihydroxyphenylglycine (**4j**).

Syntheses of penicillins (**1**～**3**) have been described previously[1,8,9]. The requisite side-chains for analogues **4a**～**4c**, **4g**, **4h** and **4j** were obtained by α-amidoalkylation procedures. Thus the reaction of resorcinol with α-hydroxyglycine derivative (**5**)[10] in acetic acid - sulfuric acid (9 : 1) gave regiospecifically (**6**) in 22% yield. Similarly, reaction of **7** (obtained from *o*-aminophenol by treatment with $MeSO_2Cl$ (1 eq) in THF-pyridine at 0°C in 82% yield) with **5** afforded arylglycine (**8**) (69%). Phenolic protection of such compounds was achieved by acetylation (Ac_2O, aq THF, pH 6); in many antibacterial screens we have found free





5 Z=$PhCH_2OOC$



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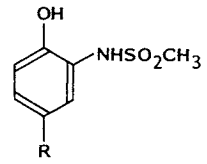
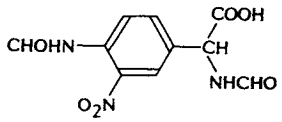


7 R=H
8 R=CH(NHZ)COOH



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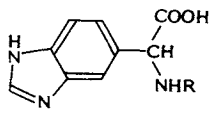
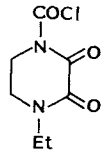


10 R=H



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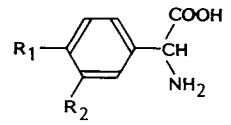
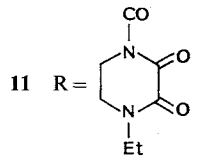
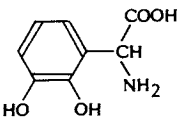


13 R_1=OH R_2=NO_2
14 R_1=NO_2 R_2=OH



11 R=



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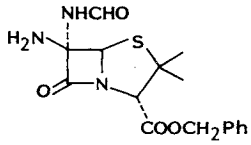

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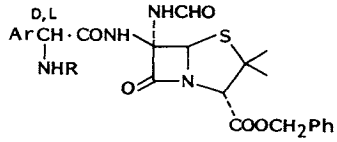

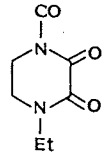

17 R=Z or

phenols and their acetates to be equiactive.

The benzimidazole series **4d** was entered by bis-*N*-formylation of DL-4-aminophenylglycine, then nitration ($HCOOH-Ac_2O$, then fuming HNO_3; 65% overall) to give acid (**9**). Catalytic hydrogenation (Pd, EtOH, HCl) followed by heating with aqueous HCOOH produced benzimidazole (**10**) (75% overall); acylation with chloride (**12**) then gave acid (**11**) (78%). The D-4-hydroxy, 3-nitro acid (**13**) is known[11]; nitration of DL-3-hydroxyphenylglycine gave the desired isomer (**14**); acylation of both these compounds with **12** gave the desired acids for **4e** and **4f**. The amino acid (**15**) was prepared by a Strecker synthesis on 2,3-dihydroxybenzaldehyde; acylation with **12**, then *O*-acetylation, gave the side-chain for **4i**.

Coupling of all side-chain acids to the 6α-formamido penicillin ester (**16**)[1] was achieved using dicyclohexylcarbodiimide (in ethyl acetate, THF, or DMF) to produce in 50~70% yield the mixed epimers of type **17**. Chromatographic separation of the desired, more polar D-epimers followed by hydrogenolysis of protecting groups (with concomitant reduction of nitro to amino in **4e** and **4f** afforded penicillins **4a**~**4j**, after acylating with chloride (**12**) where necessary, in high yield.

The antibacterial activities of the D-epimers **1**~**3** and **4a**~**4j** are shown in Table 1. It will be seen that only derivatives **4g** and **4h** which retained a 3,4-catechol exhibited activity comparable to **1**; in fact the chloro-analogue **4h** was more active than **1** against *Escherichia coli* and *P. aeruginosa* strains. The 2,3-catecholic analogue (**4i**) retained good *P. aeruginosa* activity but was otherwise 2- to 4-fold less active, while the 2,4-dihydroxy compound **4j** was very much less active. Although the isosteric analogues (**4a**~**4f**) all retained MICs of 0.25~8.0 μg/ml against Gram-negative bacteria, they were all less active than **1**, especially against *E. coli* JT425 and *P. aeruginosa*

Table 1. MICs[a] (μg/ml) of 6α-formamido, acylureido penicillins.

Organism	Derivative												
	1	**2**	**3**	**4a**	**4b**	**4c**	**4d**	**4e**	**4f**	**4g**	**4h**	**4i**	**4j**
Escherichia coli NCTC 10418	0.06	0.12	0.12	0.5	0.25	0.25	0.25	0.12	0.25	0.06	<0.03	0.12	2.0
E. coli DCO	0.25	1.0	0.25	0.5	1.0	1.0	0.5	0.5	0.5	—	<0.03	0.5	2.0
E. coli DCO RTEM	0.12	1.0	0.25	1.0	1.0	1.0	0.5	1.0	1.0	0.06	<0.03	0.5	2.0
E. coli JT425	0.25	8.0	2.0	32	8.0	8.0	4.0	4.0	4.0	0.5	0.06	2.0	8.0
Pseudomonas aeruginosa NCTC 10662	2.0	16	8.0	4.0	16	16	8.0	16	8.0	4.0	1.0	2.0	>100
P. aeruginosa K799b	0.12	2.0	1.0	2.0	—	4.0	4.0	4.0	4.0	—	0.06	0.12	—
P. aeruginosa Dalgleish (PSE-4)	1.0	8.0	4.0	4.0	16	16	8.0	16	8.0	1.0	1.0	4.0	64
Klebsiella pneumoniae T767	0.06	1.0	0.5	1.0	1.0	1.0	0.5	0.5	1.0	0.06	<0.03	1.0	4.0
Enterobacter cloacae N1	1.0	2.0	0.5	2.0	2.0	2.0	2.0	1.0	2.0	0.5	1.0	2.0	16
Proteus mirabilis 977	0.5	1.0	0.12	0.25	2.0	2.0	1.0	1.0	2.0	1.0	8.0	4.0	8.0
Staphylococcus aureus Oxford	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
Streptococcus pyogenes CN10	2.0	1.0	1.0	64	2.0	4.0	4.0	4.0	4.0	4.0	8.0	8.0	8.0

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

PSE-4. This supports the recent hypothesis[12,13] that a catechol group allows a particularly efficient transport of β-lactams across the Gram-negative outer cell wall membrane, perhaps *via* the iron-transport mechanism.

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