Pergamon

Bioorganic & Medicinal Chemistry Letters 9 (1999) 2205–2206

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

SYNTHESIS OF PYRAZOLIDINONE ANTIBACTERIAL AGENTS

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Chimie et Biologie de Substances Actives

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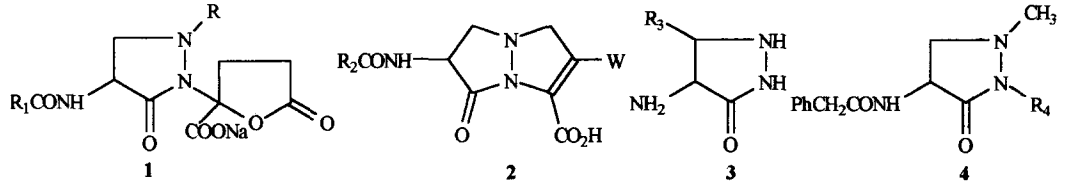
Received 3 May 1999; accepted 23 June 1999

Abstract : The synthesis of monocyclic pyrazolidinones, which show moderate antibacterial activity, are described.

Bacterial resistance to β-lactam antibiotics is increasingly worrying. More often it involves enzymes, β-lactamases[1], which catalyze the ring opening of β-lactams leading to inactive compounds. One of the possible ways for countering this resistance is to modify the β-lactam ring itself. Molecular modeling suggests that γ-lactams could replace β-lactams in the activity they exert on PBPs, penicillin-binding proteins, required for bacteria cell synthesis. Some lactivicin derivatives[4] **1** and some pyrazolidinones[2] such as **2** and **3** were described, some of them showed excellent antibacterial activity [e.g. R = CH_3, $COCH_3$, W = $COCH_3$, CN, SO_2CH_3, R_3 = H, Ph].

We have synthesised a few related monocyclic pyrazolidinones **4** and tested their biological activity against bacteria. We chose to prepare compounds possessing electron-withdrawing groups[3] (R_4) which improve the reactivity of β-lactams and the phenylacetyl side-chain of benzylpenicillin, which heightens the bindings with PBPs.



1 **2** **3** **4**

The key pyrazolidinone[4] **8** was prepared from D,L-serine methyl ester hydrochloride (**5**) which was coupled with phenylacetyl chloride to afford phenylacetylserine methyl ester (**6**). Treatment of **6** with methanesulfonyl chloride gave the acrylic acid derivative **7** which reacted with methylhydrazine and afforded the pyrazolidinone **8** in 48% overall yield from **5**.

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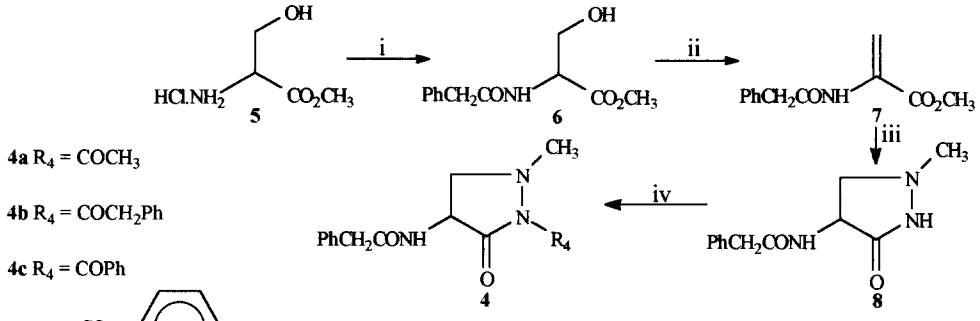
PII: S0960-894X(99)00352-2



4a $R_4 = COCH_3$

4b $R_4 = COCH_2Ph$

4c $R_4 = COPh$

4d $R_4 = CO$–(3-hydroxybenzoyl)

4e $R_4 = SO_3^-NBu_4^+$

i)$PhCH_2COCl$, Et_3N, CH_2Cl_2, RT, 16h ii) CH_3SO_2Cl, Et_3N, CH_2Cl_2, RT, 16h iii) CH_3NHNH_2, CH_2Cl_2-MeOH, 50°C, 3h iv) R_4Cl, Et_3N, CH_2Cl_2, RT, 16h or R_4OH, EEDQ, THF-MeOH, 7h or SO_3-pyridine complex, pyridine-DMF, RT, 16h

No regioisomer of **8** is observed and this is in accordance with the fact that esters react at the less substituted nitrogen, and with NMR chemical shifts[5].

Compound **8** was coupled with acetyl chloride, phenylacetyl chloride or benzoyl chloride to afford 1-methyl-2-acetyl-4-N-phenylacetamidopyrazolidin-3-one (**4a**), 1-methyl-2-phenylacetyl-4-N-phenylacetamido-pyrazolidin-3-one (**4b**) and 1-methyl-2-benzoyl-4-N-phenylacetamidopyrazolidin-3-one (**4c**) in 40% yield, 60% yield and 92% yield respectively. The coupling of **8** with 3-hydroxybenzoic acid and EEDQ gave 1-methyl-2-(3-hydroxybenzoyl)-4-N-phenylacetamidopyrazolidin-3-one (**4d**) in 40% yield. Electrophilic sulfonation of **8** with SO_3-pyridine complex gave the 1-methyl-2-sulphonyl-4-N-phenylacetamidopyrazolidin-3-one (**4e**) isolated as its tetra-n-butylammonium salt in 53% yield.

Compounds **4b** to **4e** showed moderate antibacterial activity [i.e. MICs 128 to 512 μg/ml] vs *Micrococcus luteus* and/or *Staphylococcus aureus*. In vitro qualitative microbiological testings suggested a positive synergy test of **4a**, **4b** and **4c** with cephalothin against *S. aureus* and *Escherichia coli* while **8** showed no antibacterial activity.

Acknowledgments : We thank Annick Morand for the biological studies and the Conseil Régional de Bretagne for financial support.

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