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A γ-Lactam Analogue of Penems Possessing Antibacterial Activity

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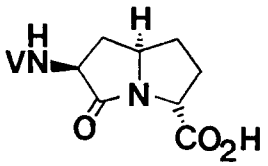
Abstract: The synthesis of a γ-lactam analogue of the penems, which showed antibacterial activity, is described.

Presently, the minimum structural requirement for antibacterial activity by antibiotics of the β-lactam family is, an appropriately activated β-lactam ring bearing a pendant carboxylic acid. In hope of discovering a new class of antibiotics related to the β-lactams, but without a β-lactam ring system we have prepared several γ-lactams, for example 1[1] and 2[2], and the literature contains several related efforts.[3] However, with the exception of a recent patent disclosure claiming antibacterial activity for the azete (3),[4] none have been shown to possess significant biological activity, either as antibacterials or as β-lactamase inhibitors.[1-3]



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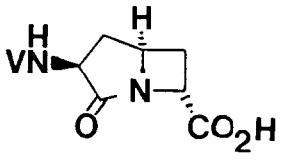

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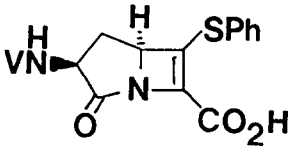

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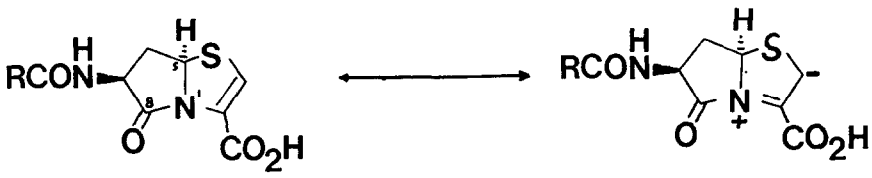
[V = $PhOCH_2CO$]

The mechanism of action of β-lactam antibiotics is believed to involve the acylation of transpeptidases involved in bacterial cell wall biosynthesis.[5] Thus the absence of antibacterial activity observed for 1 and 2 possibly derives from the lack of reactivity of the γ-lactam compared with the β-lactam ring system.[6] We reasoned a γ-lactam analogue of the 6β-acylamino penems (4),[7] might show increased reactivity and hence biological activity due to delocalisation of the lactam-N lone pair through the olefinic double bond, as in 5. In this connection it is of interest that the 6β-acylamino penems (4) have been considered too reactive for practical use as antibiotics.[8]



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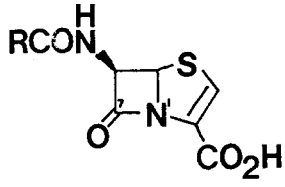

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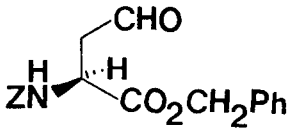
We chose cysteine and aspartic acid as readily available chiral precursors for the synthesis of 5. Thus, condensation of N-benzyloxycarbonyl-L-aspartic semi-aldehyde benzyl ester (6)[9] with L-cysteine methyl ester hydrochloride in pyridine (20°C, 5h) gave an equilibrating mixture of diastereomeric thiazolidines (7).[10] Reflux of the pyridine solution (12-15h) gave as the major product the bicyclic lactam (8)[11] (45% from 6): $[\alpha]_D^{\frac{1}{2}}$° ($CHCl_3$, c=1.48) -208°; δ_H (300MHz, $CDCl_3$) 2.41-2.48(1H, m, 6-H), 2.71-2.74(1H, m, 6-H), 3.37-3.53(2H, m, 3-H), 3.79(3H, s, OMe), 4.44-4.48(1H, m, 7-H), 5.07(1H, dd, J 8.5, 4.5Hz, 2-H), 5.14(1H, s, CH_2Ph), 5.19(1H, ca d, J 7Hz, 5-H), 5.27(1H, ca bs, NH), 7.32-7.39(5H, m, Ph). The stereochemistry of 8 at C-5 was opposite to that desired. However, reaction of D-cysteine methyl ester hydrochloride with 6, under identical conditions, gave as the major product [via



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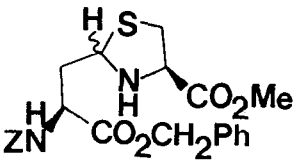

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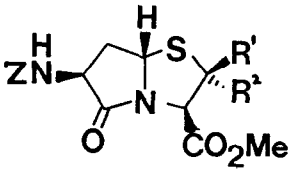
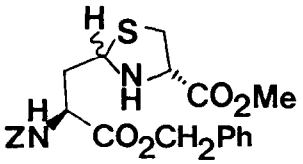


8 R_1=R_2=H
13 R_1=H, R_2=OCOPh
14 R_1=OCOPh, R_2=H



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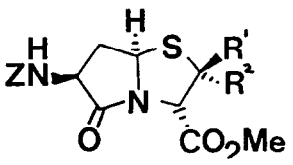
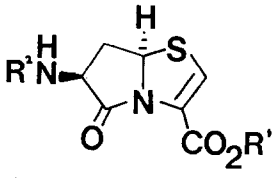
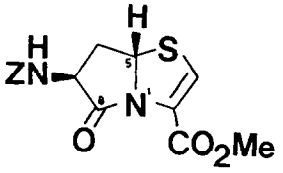


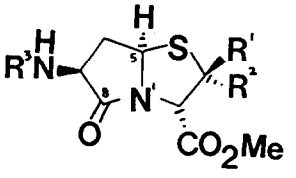
10 R_1=R_2=H
11 R_1=OCOPh, R_2=H

Functionalisation of 10 α to the sulphur atom was achieved with benzoyl peroxide[12] (benzene, reflux) to yield a single benzoate (11)[13] (40%), which on reflux in N,N-dimethylaniline (0.5h) gave the olefin (12)[14] (55%): $[\alpha]_D^{\circ}$ ($CHCl_3$, c=0.61) + 108°; ν_{max} ($CHCl_3$) 1739 s, 1721 bs cm^{-1}. Similarly reaction of 8 with benzoyl peroxide gave a 3:1 mixture of the diastereomeric benzoates (13) and (14)[13] (42% total yield). Reflux of the major benzoate (13) in N,N-dimethylaniline gave a 4:1 mixture of 12 and a new olefin (15) respectively (52% total yield).[14]

The analogue 12 was saponified [LiOH (1 equivalent), THF/H_2O][15] then dissolved in pH 7.6 50mM KH_2PO_4-K_2HPO_4-KCl buffer to give a solution of 16. The carboxylate salt (16) could be re-esterified (dimethylformamide, EtI) to the corresponding ethyl ester (17) (74% from 12), thereby proving the existence of free carboxylate (16).







12 R^1=Me, R^2=Z
16 R^1=K, R^2=Z
17 R^1=Et, R^2=Z
19 R^1=Me, R^2=V
21 R^1=K, R^2=V

15

18 R^1=R^2=H, R^3=V
20 R^1=OCOPh, R^2=H
R^3=V

[Z = $PhCH_2OCO$]
[V = $PhOCH_2CO$]

The biologically suitable phenoxyacetamido - side chain was introduced by deprotection[16] (45% HBr in AcOH) of 10, followed by reacylation ($PhOCH_2COCl$, Et_3N, dichloromethane) to give 18 (64% for 10). The olefinic linkage was introduced as before to yield 19[14] (22% from 18) via the benzoate (20), and hydrolysis (LiOH)[15] of 18 gave the desired γ-lactam analogue as the carboxylate salt (21). This salt (21) showed weak but real antibacterial activity against both gram positive bacteria (S.aureus) and gram negative bacteria (E. coli ESS).

We conclude that the bicyclic γ-lactam (21) may represent a new class of non-β-lactam antibacterials.[17]

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9. D.D. Keith, J.A. Tortora, K. Ineichen, W. Leimgruber, Tetrahedron, 1975, 31, 2633. The benzyloxycarbonyl protecting group was chosen so as to allow flexibility in the choice of side chain at a late stage of the synthesis.

10. The diastereomeric monocyclic thiazolidines (7) and (9) could be isolated in 45% and 48% yields (after chromatography) respectively from 6. ^{1}H NMR analysis of 7 and 9 showed they existed as an equilibrating mixture of diastereomers (ca 1:1). However, the overall yield of the bicyclic lactams (8) and (9) (from 6) was found to be higher without isolation of 7 or 9 respectively.

11. The relative configuration of 8 was established by NOE difference spectra, selected details (500MHz, CD_3CN/D_2O, 45°C): irradiation of βH-6 showed a 15% enhancement of αH-6 and a 15% of H-5. Irradiation of αH-6 showed a 15% enhancement of βH-6 and 20% enhancement of 7-H.

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13. The stereochemistry of the benzoates (11) (13) and (14) was elucidated from their ^{1}H NMR spectra. The coupling constant between the two vicinal thiazolidine protons for 11 and 13 was 0Hz, c.f. 7.0Hz for 14 (c.f. ref. 9).

14. The relative configurations of 12, 15 and 19 were established by NOE difference spectra; selected details: For 12 (500MHz, $CDCl_3$, 20°C): irradiation of αH-6 showed enhancements of 28% of βH-6, 8% of H-5 and 14% of H-7. For 15 (500MHz, $CDCl_3$, 20°C): irradiation of αH-6 showed enhancements of 26% of βH-6 and 12% of H-7. Irradiation of βH-6 showed enhancements of 26% of αH-6, 18% of 5-H and 2% of NH. For 19 (500MHz, $CDCl_3$, 20°C): irradiation of βH-6 showed a 26% enhancement of αH-6 and less than 2% enhancement of H-5 and H-7. Irradiation of αH-6 showed a 30% enhancement of βH-6, 10% of H-7, and 18% of H-5.

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17. After completion of this work we were informed by Dr. L. Hatfield, Eli Lilly & Co., Indianapolis, USA, that he and his colleagues have also prepared similar examples of these substances. We thank Dr. Hatfield for his communication.

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