Bioorganic & Medicinal Chemistry Letters, Vol.3, No.11, pp. 2303-2308, 1993
Printed in Great Britain

0960-894X/93 $6.00 + .00
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NEW γ-LACTAM HOMOLOGS OF PENEMS

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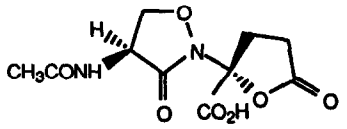
(*Received* 1 *April* 1993)

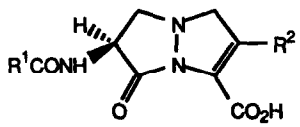
Abstract : 3-Ethylthiohomopenems 5a and 5b were prepared from α-amino-γ-butyrolactone. Compound 5a showed weak antibacterial properties.

Introduction :

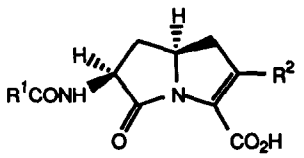
The antibacterial properties of β-lactam antibiotics result from their capacity of acylating the active serine residue of Penicillin Binding Proteins (PBPs)[1]. This has been correlated with the chemical reactivity of the β-lactam ring[2]. However, recently, much less reactive lactams such as that of naturally occurring lactivicin 1 or of synthetic pyrazolidinones 2 were shown to exhibit antibacterial activity (Scheme 1)[3-6]. Yet, the related γ-lactams 3 and 4 displayed only low levels of in vitro activity, even when electron withdrawing groups (EWGs) were introduced on the carbon-carbon double bond in order to enhance the reactivity of the γ-lactam function[7,8].



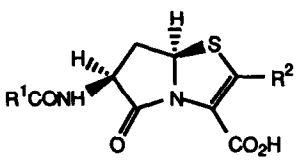
1 (lactivicin)



2 (R^2 =EWG)



3 (R^2 = H, EWG)

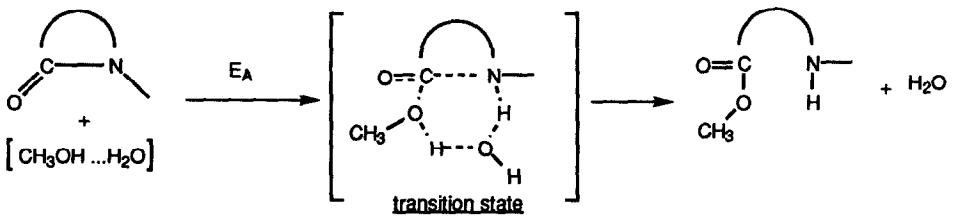


4 (R^2 = H, Alk, EWG)
5 (R^2 = SR, OR, NR2)

Scheme 1

Structural Design :

A theoretical model for the acylation step of the PBPs has recently been proposed. It stresses out the role of water molecules in a concerted process involving a proton shuttle[9]. In this model, the scissile amide bond of the inhibitor is reacted with the duplex molecule "methanol-water" mimicking the active serine residue. A six-membered transition state was considered (Scheme 2)[10]. Reactant's and transition-state's structures were fully optimized by ab initio calculation using the STO-3G minimal basis set. At the saddle point equilibrium geometry, an analytical frequencies calculation was carried out in order to analyze the components of the eigenvector associated to the negative eigenvalue of the Hessian matrix. For each molecule, this eigenvector described the reorganization of the six-memebered transition-state in the concerted methanolysis reaction. This mechanistic model indeed predicts a low activation energy (E_A) for a β-lactam fused to a five-membered ring (Table I, entry a), as well as for an isoxazolidinone related to lactivicin (entry b). Pyrazolidinones (entries c and d) are predicted to be less reactive in this model. A bicyclic γ-lactam related to the penems (entry e) shows the highest activation energy. Interestingly, the presence of an *electron-withdrawing* group on the carbon-carbon double bond does not lower the activation barrier (entry f), but a slight decrease of this barrier is observed when *electron-donating* substituents are borne by the double bond (entries g and h). We thus decided to prepare two representatives of homopenems 5 (Scheme 1, R^2 = SEt) and evaluate their biological activity.



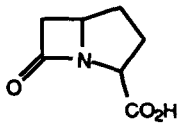
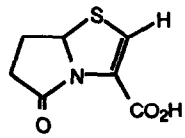
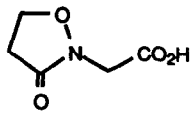
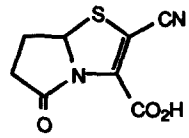
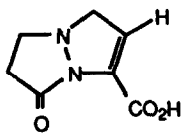
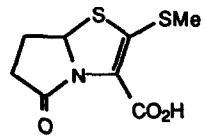
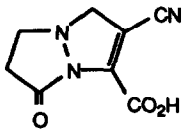
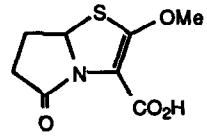
Scheme 2

Synthesis :

The synthetic plan (Scheme 3) closely follows that we had earlier applied to the synthesis of the related 2-heterosubstituted penems[11,12].

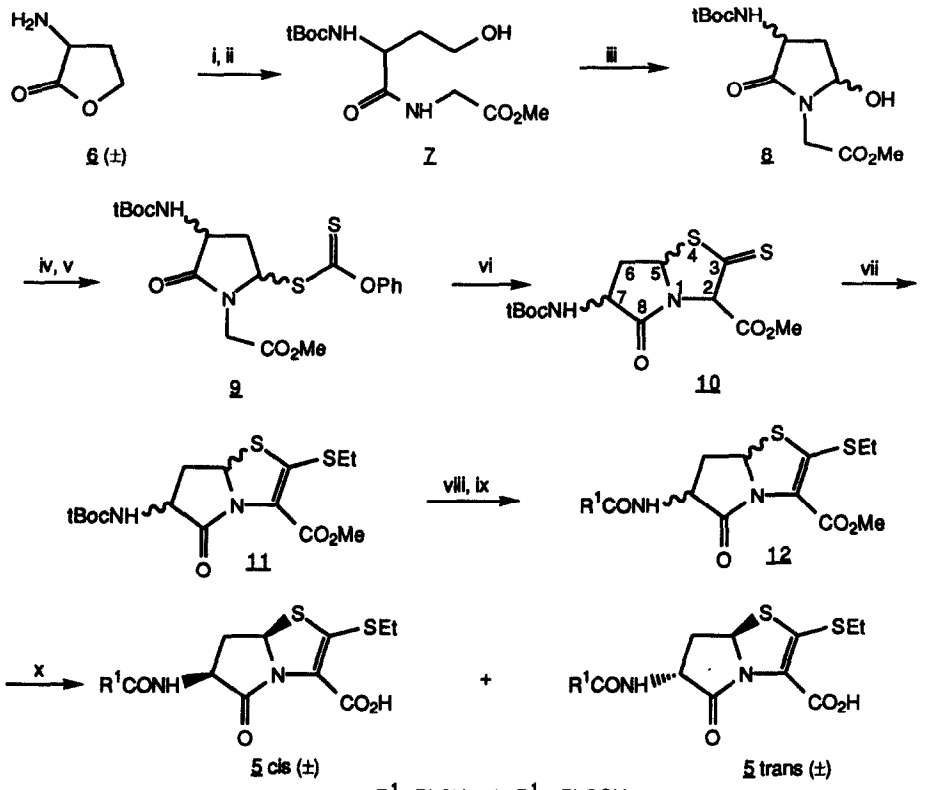
α–Amino-γ–butyrolactone (±) 6 was transformed into the corresponding t-Boc derivative which was reacted with an excess of methyl glycinate to give 7[13].

Table 1 : Calculated Activation Energies

	Structure	E_A (kcal/mole)		Structure	E_A (kcal/mole)
a		16.039	e		22.008
b		17.926	f		22.138
c		20.762	g		21.551
d		19.500	h		20.900

Swern oxidation yielded an aldehyde which spontaneously cyclized to form a 3 : 1 mixture of cis and trans 5-hydroxy-2-pyrolidinone 8[14]. Substitution of the hydroxyl group by a thiol group was easily effected with hydrogen sulfide in the presence of a catalytic amount of p-toluensulfonic acid. Acylation of the resulting thiol (cis : trans mixture 1 : 3) with phenyl chlorothiocarbonate yielded a mixture of cis and trans dithiocarbonates 9 which could be separated by chromatography on silica gel (dichloromethane : ethylacetate 95 : 5; yields : cis, 13 %; trans 44 %). Each isomer or the mixture of isomers could be cyclized to the bicyclic γ-lactams 10 by treatment with lithium hexamethyldisilazide (yields 62-70 %)[15]. They could be readily converted into the corresponding homopenems 11 by alkylation with ethyliodide in the presence of triethylamine. When the sequence (v-vii; Scheme 3) was performed on the cis : trans mixture of isomers, without separations at any stages, a 1 : 3 mixture of cis and trans homopenems 11 was obtained.

A sample of each isomer was isolated by chromatography on silica gel (dichloromethane : ethylacetate 90 : 10) and characterized without ambiguity.



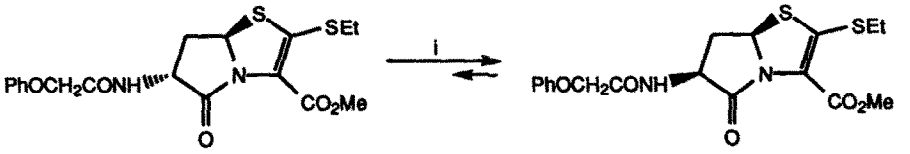
a, $R^1 = PhCH_2$; b, $R^1 = PhOCH_2$

(i) $(tBoc)_2O$, Et_3N, CH_2Cl_2, , 75%; (ii) $Cl^- H_3N^+ - CH_2CO_2Me$, Et_3N, 65°C, 74%; (iii) $(COCl)_2$, DMSO, Et_3N, -70°Cto 0°C, 74%; (iv) H_2S, p-TsOH cat., CH_2Cl_2, 0°C, 96%; (v) ClC(S)OPh, Et_3N, CH_2Cl_2, 0°C, 57%; (vi) LiHMDS (4equiv.), THF, -15°C to 0°C, 62-70%; (vii) EtI, Et_3N,CH_2Cl_2, 20°C, 73%; (viii) TFA, CH_2Cl_2, 0°C, 100%; (ix) NEt_3,R^1COCl, CH_2Cl_2, 70-77%; (x) $AlCl_3$, EtSH, CH_2Cl_2, 20°C, 90% for 5a and 75% for 5b.

Scheme 3

Treatment of the mixture of isomers 11 with trifluoroacetic acid followed by acylation with the appropriate acid chloride in the presence of triethylamine yielded a cis : trans (~ 1 : 3) mixture of 7-acylamino-homopenems 12[16]. The free acids 5a and 5b were obtained by treatment of the methyl esters with ethanethiol in the presence of aluminium trichloride[17].

This synthetic scheme (Scheme 3) provides an easy access to homopenems of type 5 (R^2 = SR). The lack of stereoselectivity was not particularly harmful because the unwanted methyl esters 12 trans could be readily equilibrated to give a mixture containing more than 82 % of the desired cis isomer (Scheme 4).



12b (trans) 12b (cis)

(i) DBN, CH_2Cl_2, 20°C, 2h.

Scheme 4

Biological studies :

Homopenems 5 cis and 5 trans were tested in vitro against representative gram-positive and gram-negative bacteria[18]. The cis : trans (1 : 4) mixture of 5a showed weak antibacterial properties : MIC = 320 µg/ml (S. aureus). This level of activity is in the range of that reported for other γ-lactams. At 100 µM concentration, it also gave 15 % inhibition of the isolated D,D-carboxypeptidase from Actinomadura R39[19]. Neither 5a nor 5b were inhibitors of representative β–lactamases[20]. Thus, the presence of a thioether group on the double bond of the homopenems does not improve the biological properties of the system.

Acknowledgments : This work was generously supported by the "Ministère de la Région Wallonne, Direction Générale des Technologies, de la Recherche et de l'Énergie" (convention MTLGG156/dos. 1810/07.10.91), the "Fonds National de la Recherche Scientifique" (Belgium) and SmithKline Beecham (Brockham Park, U.K.). We thank SmithKline Beecham for the biological evaluations.

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15. Methyl (5,7 cis)-1-aza-8-oxo-7-t-butoxycarbonylamino-4-thia-3-thioxo-bicyclo[3.3.0]octane-2-carboxylate 10 : IR (CH_2Cl_2) ν 1743, 1718 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 6.30 (ABX m, 1 J = 8.5 Hz, H-5), 5.51 (s, 1, H-2), 5.15-5.00 (m, 1, NH), 4.40-4.20 (m, 1, H-7), 3.83 (s, 3, OCH_3), 3.05-2.85 (m, 1, H-6), 2.80-2.65 (m, 1, H'-6), 1.48 (s, 9, tBu); ^{13}C-NMR (50 MHz, $CDCl_3$) ppm 228.77(C-3), 174.77 (C-8), 164.75 (CO ester), 156.00 (CO carbamate), 80.86 ($\underline{C}Me_3$), 77.76 (C-2), 71.31 (C-5), 53.53 (OMe), 51.23 (C-7), 29.79 (C-6), 28.21 (tBu); Mass (FAB) m/e 347 $(M+1)^{+\cdot}$, 291, 247, 231, 259, 225; Anal. $C_{13}H_{18}N_2O_5S_2$-calcd : %C, 45.07; %H, 5.24; %N, 8.09 - Found : %C, 44.82; %H, 5.30; %N, 8.07; mp 171°C; t.l.c. (SiO_2, EtOAc-CH_2Cl_2 40:60) Rf = 0.44.
(5,7 trans) 10 : ^{1}H-NMR (200 MHz, $CDCl_3$) δ 6.11 (t, 1, J = 7 Hz, H-5), 5.55 (s, 1, H-2), 5.15 (br s, 1, NH), 4.65-4.50 (m, 1, H-7), 3.83 (s, 3, OCH_3), 3.50-3.25 (m, 1, H-6), 2.50-2.30 (m, 1, H'-6), 1.45 (s, 9, tBu); t.l.c. (SiO_2, EtOAc-CH_2Cl_2 40:60) Rf = 0.30.
16. Methyl (5,7 cis)-1-aza-3-ethylthio-8-oxo-7-phenylacetamido-4-thia-bicyclo[3.3.0]oct-2-en-2-carboxylate 12a : IR (CH_2Cl_2) ν 1730 (br), 1680 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.40-7.25 (m, 5, Ph), 6.30 (br d, 1, J = 5 Hz, NH), 5.80 (t, 1, J = 6.5 Hz, H-5), 4.81-4.68 (m, 1, H-7), 3.79 (s, 3, OCH_3), 3.62 (s, 2, CH_2-CONH), 3.40-3.25 (m, 1, H-6), 2.97-2.87 (ABX$_3$ m, 2, J = 7.4 Hz, S-$\underline{CH_2}$-CH_3), 2.30-2.15 (m, 1, H'-6), 1.35 (ABX$_3$ m, 3, J = 7.4 Hz, S-CH_2-$\underline{CH_3}$); ^{13}C-NMR (50 MHz, $CDCl_3$) ppm 171.59 (C-8), 171.41 (CO amide), 159.58 (CO ester), 147.20 (C-3), 134.25, 128.81, 128.41, 127.22, 116.27 (C-2), 66.13 (C-5), 51.94 (OMe), 51.50 (C-7), 43.00 (Ph$\underline{C}H_2$), 35.84 (C-6), 29.82 (S-$\underline{CH_2}$), 14.79 (S-CH_2-$\underline{CH_3}$); Mass (FAB) m/e 393 $(M+1)^{+\cdot}$, 361, 333, 305, 299, 289, 273; t.l.c. (SiO_2, EtOAc-CH_2Cl_2 20:80) Rf = 0.20.
(5,7 trans) 12a : ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.40-7.25 (m, 5, Ph), 6.40 (br d, 1, J = 6.4 Hz, NH), 5.86 (dd, 1, J = 7 and 1 Hz, H-5), 4.81-4.68 (m, 1, H-7), 3.80 (s, 3, OCH_3), 3.60 (s, 2, CH_2CONH), 3.04-2.85 (m, 1, H-6), 2.99-2.93 (ABX$_3$ m, 2, J = 7.4 Hz, S-$\underline{CH_2}$-CH_3), 2.42-2.25 (ddd, 1, J = 17,8 and 7 Hz, H'-6), 1.36 (ABX$_3$ m, 3, J = 7.4 Hz, S-CH_2-$\underline{CH_3}$); t.l.c. (SiO_2, EtOAc-CH_2Cl_2 20:80) Rf = 0.32.
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