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Introduction of a pyrrole cycle in cephalosporine structures as approach in the search for new beta-lactame antibiotics

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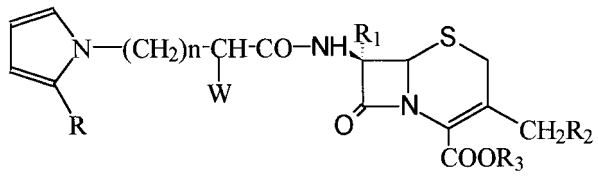
12 New cephalosporines containing a pyrrole cycle in the N-acyl chain have been synthesized based on N-acylation of 7-ACA or of its 3′-analogues via the mixed anhydrides of substituted pyrrole carboxylic acids, and following two types of procedure. Confirming ^{1}H NMR and IR data are represented. The preliminary microbiological tests *in vitro* show significant antibacterial activity in some cases compared with that of cefalexin. Some common structure-activity relationships have been observed.

1. Introduction

One of the approaches in the search for new beta-lactame antibiotics, is the modification of the N-acyl chain in the known active structures by different heterocycles. Pyrrole proved to be relatively rarely involved in these investigations, and the few typical new pyrrole containing antibiotics [1–3] could be generalized with the following formula:



where n is 0–3; W could be H, 1–5 C-alkyl, SO_3H, or alyphatic acid chain; R is H or CHO, R_1 is H or MeO; R_2 is 1,3,4-thiadiazol-2-ylthio, tetrazol-5-ylthio, 1,3,4-oxadiazol-2-ylthio or 1,2,3-triazol-5-ylthio; R_3 is H, NH_4, cation or ester residue.

In some of our previous announcements about new pyrrole-containing penicillins we reported on promising antibacterial activity [4–6].

In the present study the same idea was spread over the group of cephalosporines and some relationships between the chemical structure and the microbiological effects were also estimated.

Table 1: Comparative *in vitro* activity of the new cephalosporin products (method I)

Compd.	Diameter of sterile zones (mm)					
	Staph. aureus 209			*E. coli* 125-III-0		
	1000	100	10	1000	100	10
4h	34	24	18	19	12.5	10
4i	26	17	15	34	33	25
4k	18	16	10	44	41	28
4l	35	27	21	17	10	5
4m	36	29	24	20	17	10
4n	22	18	11	35	28	20
6r	25	17	11	17	10	5
6s	22	14	10	19	15	8
6t	12	10	7	24	19	14
6u	28	24	19	16	12	10
6v	28	23	14	18	17	11
6w	19	17	12	25	23	19

2. Investigations and results

2.1. Chemistry

Two series of six substituted pyrrole beta-carboxylic acids have been used as N-acylating agents and carriers of the pyrrole structure, each differing by the presence or absence of a benzyl residue at the pyrrole N-atom. 7-Aminocephalosporanic acid (7-ACA) and two of its 3-substituted analogues have been chosen as beta-lactame partners. The pyrrole parts of the molecules are related to some known structures with a variety of biological activities, which additionally motivates the interest in the target products.

Both series of 12 new cephalosporines have been synthesized via mixed anhydrides [7–9] following the general reaction Schemes 1 and 2. N-benzyl-substituted derivatives are obtained in a water containing organic solvent in the conditions of Shotten-Bauman [10] and the N-nonsubstituted analoga – in dry medium (methylene chloride) after preliminary silylation of the beta-lactame partner, offering higher average yields (60% against 43%, according to the first procedure).

The structures of the new cephalosporin products are supported by their NMR and IR spectra (see Experimental).

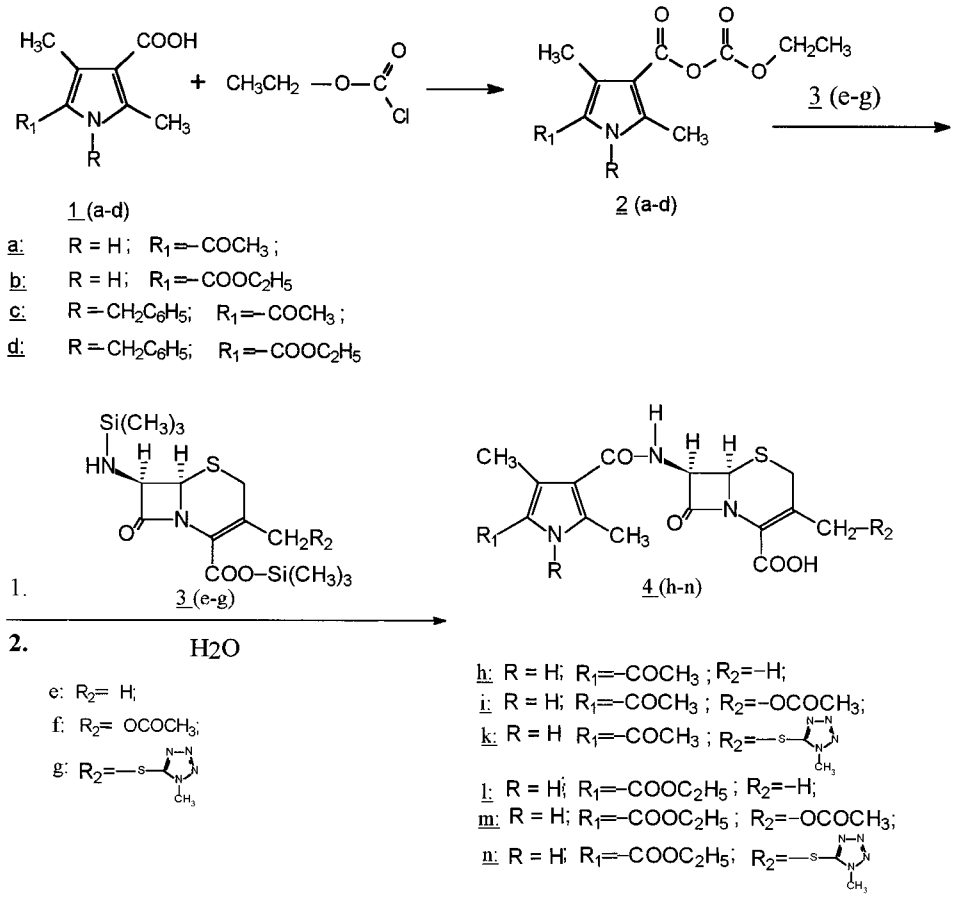
The starting pyrrole carboxylic acids are known products available in high yields by hydrolysis of the pyrrole esters

Table 2: Comparative *in vitro* activity of the new compounds (method II)

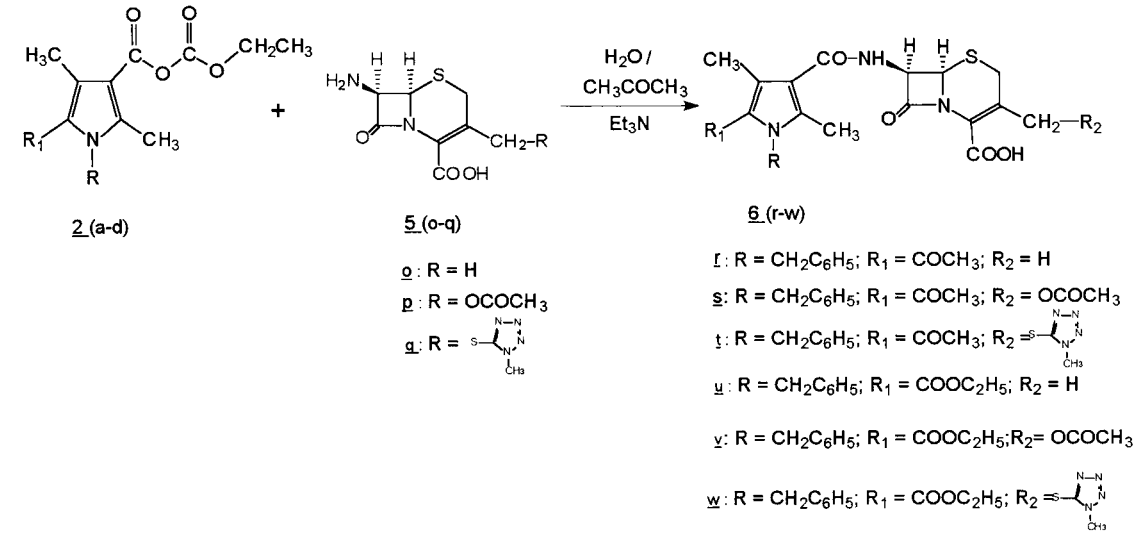
Compd.	MIC (μg/cm^3)	
	Staph. aureus 209	*E. coli* 125-III-0
4h	0.156	25
4i	0.31	12.5
4k	12.5	0.156
4l	0.15	12.5
4m	0.15	6.25
4n	12.5	1.56
6r	0.31	25
6s	6.25	12.5
6t	25	1.56
6u	0.31	12.5
6v	6.25	6.25
6w	12.5	3.12

[11, 12], obtained by the classical Knorr procedure [13, 14] based on the corresponding beta-dicarbonyl compounds. N-benzylation has been carried out with benzylchloride in dry tetrahydrofurane via N–Na salt of the pyrrole esters [15]. 7-ACA and its 3-substituted analoga are commercial products.

Scheme 1



Scheme 2



2.2. Microbiological studies

Two types of preliminary microbiological studies of the new cephalosporine products have been carried out *in vitro* using *Staph. aureus* 209 as a Gram positive strain and *E. coli* 125-111-0 as a Gram negative one. The results of the diffusion method in agar (Rendal medium) are presented in Table 1, those of the doubled serial dilution method (Mueller-Hinton medium) in Table 2.

3. Discussion

The results can be generalised as follows:

- All the 12 investigated new cephalosporines show antibacterial activity and in 6 of the cases the minimum inhibiting concentrations (MIC) being observed come in the range of 3.1 to 0.15 μg/cm^3 (or even lower) and are commensurate with those of cefalexin used under the same conditions as a reference antibiotic.
- The products with a N-unsubstituted pyrrole cycle show significantly higher (up to several times) activity compared with the corresponding N-benzylated derivatives, keeping the nature of the rest of the substituents the same.
- The replacement of 3′-acetoxymethyl- or 3′-methyl groups with a 3′-[(1-methyl-1 *H*-1,2,3,4-tetrazol-5-yl)-sulfanyl]methyl- residue leads to a higher specific activity against the Gram (−) test strain, while the activity against *Staph. aureus* 209 decreases.
- The nature of the rest of the substituents in the pyrrole cycle does not influence the antibacterial activity significantly.

4. Experimental

4.1. Method A

4.1.1. Silylation of 3′-substituted derivatives of 7-aminocephalosporanic acid to **3e–g** *(general procedure)*

Triethylamine (0.015 mol) was added to a stirred suspension of 0.01 mol of the corresponding cephalosporanic acid derivative in 25 ml dry dichloroethan at 8–10 °C. After 15 min, trimethyl-chlorsilan (0.025 mol) was added dropwise and the temperature was slowly increased to 25 °C. The mixture was stirred for 30 min at this temperature and for 1 h at 50 °C and then filtered from the triethylammoniumchloride. The obtained silyl derivative remains in the filtrate and does not need to be isolated or purified for later use.

4.1.2. Mixed anhydrides of 2,4-dimethyl-3-carboxylic acids of the pyrrol derivatives **1a–d** *(general procedure)*

Triethylamine (0.015 mol) was added at once to a stirring suspension of 0.01 mol of the corresponding pyrrolecarboxilic acid in 25 ml dry dichloroethan. The mixture was cooled to −10–−12 °C and at the same temperature 0.015 mol ethylchlorometanoate in 10 ml dry dichloroethan was added dropwise for 30 min then stirred for 45 min at the same temperature and filtered from the triethylammoniumchloride. The obtained mixed anhydride remains in the filtrate and does not need to be isolated or purified for the later acylation procedure.

4.1.3. Acylation of the silylated 3′-substituted derivatives of 7-aminocephalosporanic acid to **4h–n** *(general procedure)*

To a cooled −12–−15 °C suspension of the obtained mixed anhydride of the corresponding pyrrolecarboxilic acids **2a–d** a solution of the silylated corresponding cephalosporanic acids **3e–g** was added dropwise for 30 min under intensive stirring. The reaction temperature was allowed to rise to 5 °C where it was maintained for 1 h. The mixture was stirred intensively at room temperature for 8 h to complete the reaction. The obtained suspension was filtered to remove the portions of triethylaminohydrochloride. Then the resulting filtrate was stirred with an equal volume of water for 1 h. The organic layer was washed 2–3 times with water and dried over anh. sodium sulfate. The solution was filtered and evaporated under diminished pressure to dryness. The residue was dissolved in dry ethyl acetate and the product was isolated after adding n-hexane.

4.2. Method B

4.2.1. Acylation of 3′-substituted derivatives of 7-aminocephalosporanic acid **5o–q** *in organic solvent/water medium by Shotten-Baumann method (general procedure)*

To a cooled (0–5 °C), stirred suspension of 0.01 mol of the corresponding cephalosporanic acid in 12.5 ml of water and 51 ml of acetone, 0.015 mol triethylamine was added dropwise until a clear solution was obtained. The resulting solution was added dropwise for 1 h to the suspension containing the mixed anhydride of the corresponding pyrrolecarboxilic acid **2a–d**, and cooled to −12–−15°C. The obtained mixture was intensively stirred at −10 °C for 30 min, then allowed to warm to 0 °C for 2 h. Then the reaction mixture was stirred 1–8 h at room temperature and evaporated under reduced pressure to dryness. The resulting residue was taken up in 50 ml water and 50 ml ethyl acetate. Under intensive stirring and at a temperature of 5 °C the pH of the suspension was adjusted to about 2.0 with equimolar amounts of 4 N hydrochloric acid and then the aqueous phase was separated and extracted twice with ethyl acetate. The ethyl-acetate extractions were dried over magnesium sulfate and evaporated under diminished pressure to afford 25 ml of residue. The product was isolated as an acid adding n-hexane.

4.3. Product characteristics

4.3.1. (7 R)-7-({[5-(Acetyl)-2,4-dimethyl-1 H-3-pyrrolyl]carbonyl}amino)-3-(methyl)-6-oxo-7,7α-dihydro-2 H,6 H-azeto[2,1-β][1,3]thiazine-4-carboxylic acid (**4h**)

M.p. 204 °C; N-Acylation procedure: A, −10 °C, 2 h; yield 58%. ^{1}H NMR (d_6-DMSO): 2.3 (s, 3 H, $COCH_3$); 2.4 (2 × s, 6 H, 2 CH_3); 12.1 (s, 1 H, OH); 1.9 (s, 3 H, $CH_3(3')$); 4.6 (d, 1 H, H(5)); 4.9 (d, 1 H, H(6)); 3.3 (d, 2 H, $CH_2(2)$); 6.25 (d, 1 H, N-CONH). IR (KBr): 1200 (C−O−C); 1385 (CH_3); 1695 (amide I); 1545 (amide II); 1760 (β-lactam); 1660 ($COCH_3$); 2450–2850 (COOH); 3000–3100 (NH + OH).

4.3.2. (7 R)-7-({[5-(Acetyl)-2,4-dimethyl-1 H-3-pyrrolyl]carbonyl}amino)-3-[(acetoxy) methyl]-6-oxo-7,7α-dihydro-2 H,6 H-azeto[2,1-β] [1,3] thiazine-4-carboxylic acid (**4i**)

M.p. 224–225 °C; N-Acylation procedure: A, −12 °C, 4 h; yield 52%. ^{1}H NMR (d_6-DMSO): 2.5 (2 × s, 6 H, 2 CH_3); 4.85 (d, 1 H, H(5)); 4.95 (d, 1 H, H(6)); 2.3 (s, 3 H, $COCH_3$); 12.5 (s, 1 H, OH); 1.0 (s, 3 H, $CH_3(3')$); 3.4 (d, 2 H, $CH_2(3')$); 6.1 (d, 2 H, CH(2)); 6.25 (d, 1 H, N-CONH). IR (KBr): 1645–1675 (amide I); 1545–1570 (amide II); 1760–1770 (β-lactam); 1250 (C−O−C); 1375 (CH_3); 1645–1665 ($COCH_3$); 2450–2800 (COOH); 3000–3100 (NH + OH).

4.3.3. (7 R)-7-({[5-(Acetyl)-2,4-dimethyl-1 H-3-pyrrolyl]carbonyl}amino)-3-{[(1-methyl-1 H-1,2,3,4-tetrazol-5-yl)sulfanyl]methyl}-6-oxo-7,7α-dihydro-2 H, 6 H-azeto[2,1-β][1,3]thiazine-4-carboxylic acid (**4k**)

M.p. 169–170 °C; N-Acylation procedure: A, −14 °C, 8 h; yield 50%. ^{1}H NMR (d_6-DMSO): 3.85 (s, 3 H, $CH_3(3')$); 2.4 (2 × s, 6 H, 2 CH_3); 2.3 (s, 3 H, $COCH_3$); 3.6 (d, 2 H, $CH_2(3')$); 4.6 (d, 1 H, H(5)); 4.8 (d, 1 H, H(6)); 12.0 (s, 1 H, OH); 4.2 (d, 2 H, $CH_2(2)$); 5.8 (d, 1 H, N−CO−NH). IR (KBr): 1375 (CH_3); 1645–1665 ($COCH_3$); 2450–2800 (COOH); 1230–1250 (C−O−C); 1645–1675 (amide I); 1545–1580 (amide II); 1760–1765 (β-lactam); 3000–3200 (NH + OH).

4.3.4. (7 R)-7-({[5-(Ethoxycarbonyl)-2,4-dimethyl-1 H-3-pyrrolyl]carbonyl}amino)-3-(methyl)-6-oxo-7,7α-dihydro-2 H,6 H-azeto[2,1-β][1,3]thiazine-4-carboxylic acid (**4l**)

M.p. 198 °C; N-Acylation procedure: A, −10 °C; 2.5 h; yield 60%. ^{1}H NMR (d_6-DMSO): 1.32 (t, 3 H, $CH_2\underline{CH_3}$); 4.2 (q, 2 H, $\underline{CH_2}CH_3$); 12.5 (s, 1 H, OH); 1.9 (s, 3 H, $CH_3(3')$); 2.45 (2 × s, 6 H, 2 × $\overline{CH_3}$); 4.6 (d, 1 H, H(5)); 4.8 (d, 1 H, H(6)); 3.3 (d, 2 H, $CH_2(2)$); 5.8 (d, 1 H, N−CO−NH). IR (KBr): 1695 ($COOC_2H_5$); 1375 (CH_3); 1250–1260 (C−O−C); 1760 (β-lactam); 1510–1560 (amide II); 1640–1665 (amide I); 2500–2800 (COOH); 3000–3100 (NH + OH).

4.3.5. (7 R)-7-({[5-(Ethoxycarbonyl)-2,4-dimethyl-1 H-3-pyrrolyl]carbonyl}-amino)-3-[(acetoxy)methyl]-6-oxo-7,7α-dihydro-2 H,6 H-azeto[2,1-β]-[1,3]thiazine-4-carboxylic acid (**4m**)

M.p. 211–212 °C; N-Acylation procedure: A, −12 °C, 3 h; yield 54%. ^{1}H NMR (d_6-DMSO): 2.0 (s, 3 H, $CH_3(3')$); 1.25 (t, $CH_2\underline{CH_3}$); 4.2 (q, 2 H, $\underline{CH_2}CH_3$); 3.5 (d, 2 H, $CH_2(3')$); 2.5 (2 × s, 6 H, 2 $\overline{CH_3}$); 6.1 (d, 1 H, $\overline{N-CO-NH}$); 6.0 (d, 2 H, $CH_2(2)$); 12.4 (s, 1 H, OH); 4.7 (d, 1 H, H(5)); 4.9 (d, 1 H, H(6)). IR (KBr): 1250–1260 (C−O−C); 1370–1380 (CH_3); 1645–1665 (amide I); 1510–1560 (amide II); 1760–1765 (β-lactam); 1685–1690 ($COOC_2H_5$); 3000–3100 (NH + OH); 2450–2850 (COOH).

4.3.6. (7 R)-7-({[5-(Ethoxycarbonyl)-2,4-dimethyl-1 H-pyrrolyl]carbonyl}-amino)-3-{[(1-methyl-1 H-1,2,3,4-tetrazol-5-yl)sulfanyl]methyl}oxo-7,7α-dihydro-2 H,6 H-azeto[2,1-β][1,3]thiazine-4-carboxylic acid (**4n**)

M.p. 261–262 °C; N-Acylation procedure: A, −10 °C, 2 h; yield 49%. ^{1}H NMR (d_6-DMSO): 3.8 (s, 3 H, $CH_3(3')$); 1.2 (t, 3 H, $CH_2\underline{CH_3}$); 4.2 (q, 2 H, $\underline{CH_2}CH_3$); 2.5 (2 × s, 6 H, 2 CH_3); 4.7 (d, 1 H, H(5)); 4.82 (d, 1 H, H(6)); 3.58 (d, 2 H, $CH_2(3')$); 6.4 (d, 1 H, N−CO−NH); 6.42 (d, 2 H, $CH_2(2)$); 12.5 (s, 1 H, OH). IR (KBr): 1645–1675 (amide I); 1510–1560 (amide II); 1760–1770 (β-lactam); 1245–1255 (C−O−C); 1380 (CH_3); 1685–1695 ($COOC_2H_5$); 2450–2800 (COOH); 3000–3100 (NH + OH).

4.3.7. (7 R)-7-({[1-Benzyl-5-(acetyl)-2,4-dimethyl-1 H-3-pyrrolyl]carbonyl}-amino)-3-(methyl)-6-oxo-7,7α-dihydro-2 H,6 H-azeto[2,1-β][1,3]thiazine-4-carboxylic acid (**6r**)

M.p. 216–218 °C; N-Acylation procedure: B, −10 °C, 2 h; yield 49%. ^{1}H NMR (d_6-DMSO): 6.9–7.2 (2 × d, 5 H, C_6H_5-R); 2.5 (2 × s, 6 H, 2 CH_3); 2.25 (s, 3 H, $COCH_3$); 2.0 (s, 3 H, $CH_3(3')$); 3.45 (d, 2 H, $CH_2(2)$); 5.5 (s, 2 H, $\underline{CH_2}-C_6H_5$); 4.85 (d, 1 H, H(5)); 4.95 (d, 1 H, H(6)); 6.25 (d, 1 H, N−CO−NH); 12.5 (s, 1 H, OH). IR (KBr): 1640–1685 (amide I); 1545–1565 (amide II); 1760 (β-lactam); 1250 (C−O−C); 700–750 (R−C_6H_5); 1640–1675 ($COCH_3$); 2400–2800 (COOH).

4.3.8. (7 R)-7-({[1-Benzyl-5-(acetyl)-2,4-dimethyl-1 H-3-pyrrolyl]carbonyl}-amino)-3-[(acetoxy)methyl]-6-oxo-7,7α-dihydro-2 H,6 H-azeto[2,1-β][1,3]-thiazine-4-carboxylic acid (**6s**)

M.p. 186–189 °C; N-Acylation procedure: B, −12 °C, 4 h; yield 45%. ^{1}H NMR (d_6-DMSO): 6.8–7.1 (2 × d, 5 H, C_6H_5-R); 1.8 (s, 3 H, $CH_3(3')$); 2.4 (2 × s, 6 H, 2 CH_3); 2.25 (s, 3 H, $COCH_3$); 3.3 (d, 2 H, $CH_2(3')$); 4.5 (d, 1 H, H(5)); 4.8 (d, 1 H, H(6)); 5.5 (s, 2 H, $\underline{CH_2}-C_6H_5$); 12.3 (s, 1 H, OH); 5.6 (d, 2 H, $CH_2(2)$); 5.65 (d, 1 H, N−CO−HN). IR (KBr): 1645–1675 (amide I); 1510–1550 (amide II); 1760 (β-lactam); 1250 (C−O−C); 1375 (CH_3); 1680–1695 ($COCH_3$); 2450–2800 (COOH); 700–750 (R-C_6H_5).

4.3.9. (7 R)-7({[1-Benzyl-5-(acetyl)-2,4-dimethyl-1 H-3-pyrrolyl]carbonyl}-amino)-3-{[(1-methyl-1 H-1,2,3,4-tetrazol-5-yl)sulfanyl]methyl}-6-oxo-7,7α-dihydro-2 H,6 H-azeto[2,1-β][1,3]thiazine-4-carboxylic acid (**6t**)

M.p. 207–209 °C; N-Acylation procedure: B, −12 °C, 8 h; yield 43%. ^{1}H NMR (d_6-DMSO): 3.8 (s, 3 H, $CH_3(3')$); 2.3–2.4 (2 × s, 6 H, 2 CH_3); 2.2 (s, 3 H, $COCH_3$); 3.52 (d, 2 H, $CH_3(3')$); 6.0 (d, 2 H, $CH_2(2)$); 4.6 (d, 1 H, H(5)); 4.8 (d, 1 H, H(6)); 6.05 (d, 1 H, N−CO−NH); 5.42 (s, 2 H, $\underline{CH_2}-C_6H_5$); 12.6 (s, 1 H, OH); 6.78–7.0); 2 × d, 5 H, C_6H_5-R); 4.2 (d, 2 H, $CH_2(2)$). IR (KBr): 1640–1665 (amide I); 1545–1550 (amide II); 1225 (C−O−C); 1375 (CH_3); 1760–1785 (β-lactam); 720–750 (R−C_6H_5); 1685–1690 ($COCH_3$); 2800 (COOH).

4.3.10. (7 R)-7-({[1-Benzyl-5-(ethoxycarbonyl)-2,4-dimethyl-1 H-3-pyrrolyl]-carbonyl}amino)-3-(methyl)-6-oxo-7,7α-dihydro-2 H, 6 H-azeto[2,1-β][1,3]-thiazine-4-carboxylic acid (**6u**)

M.p. 280–281 °C; N-Acylation procedure: B, −10 °C, 3 h; yield 49%. ^{1}H NMR (d_6-DMSO): 1.1 (t, 3 H, $CH_2\underline{CH_3}$); 4.1 (q, 2 H, $\underline{CH_2}CH_3$); 12.5 (s, 1 H, OH); 2.3–2.4 (2 × s, 6 H, 2 × $\overline{CH_3}$); 4.6 (d, 1 H, $\overline{H(5)}$); 4.8 (d, 1 H, H(6)); 6.7–7.0/2 × d, 5 H, C_6H_5-R); 3.5 (d, 2 H, $CH_2(2)$); 5.6 (d, 1 H, N−CO−NH); 5.5 (s, 2 H, $\underline{CH_2}-C_6H_5$); 3.8 (s, 3 H, $CH_3(3')$). IR (KBr): 1685 ($COOC_2H_5$); 1380 ($\overline{CH_3}$); 1250–1260 (C−O−C); 1760 (β-lactam); 1530–1545 (amide II); 1630–1655 (amide I); 2400–2800 (COOH); 3000–3100 (NH + OH).

4.3.11. (7 R)-7-({[1-Benzyl-5-(ethoxycarbonyl)-2,4-dimethyl-1 H-3-pyrrolyl]-carbonyl}amino)-3-[(acetoxy)methyl]-6-oxo-7,7-α-dihydro-2 H, 6 H-azeto-[2,1-β][1,3]thiazine-4-carboxylic acid (**6v**)

M.p. 257–258 °C; N-Acylation procedure: B, −10 °C, 5 h; yield 47%. ^{1}H NMR (d_6-DMSO): 3.2 (s, 3 H, $CH_3(3')$); 1.0 (t, 3 H, $CH_2\underline{CH_3}$); 4.0 (q, 2 H, $\underline{CH_2}CH_3$); 3.0 (d, 2 H, $CH_2(3')$); 2.0–2.1/2 × s, 6 H, 2 $\overline{CH_3}$); 4.8 (d, 1 H, $\overline{N}-CO-NH$); 4.7 (d, 2 H, $CH_2(2)$); 3.4 (d, 1 H, H(5)); 3.5 (d, 1 H, H(6)); 4.6 (s, 2 H, $\underline{CH_2}-C_6H_5$); 12.1 (s, 1 H, OH); 5.75–6.05/2 × d, 5 H, C_6H_5-R/. IR (KBr): 1250 (C−O−C); 1370–1380 (CH_3); 1640–1665 (amide I); 1695 ($COOC_2H_5$); 1540–1565 (amide II); 1760–1770 (β-lactam); 3000–3100 (NH + OH); 2450–2850 (COOH).

4.3.12. (7 R)-7-({[1-Benzyl-5-(ethoxycarbonyl)-2,4-dimethyl-1 H-3-pyrrolyl]-carbonyl}amino)-3-{[(1-methyl-1 H-1,2,3,4-tetrazol-5-yl)sulfanyl]methyl}-6-oxo-7,7α-dihydro-2 H,6 H-azeto[2,1-β][1,3]thiazine-4-carboxylic acid (**6w**)

M.p. 149–150 °C; N-Acylation procedure: B, −12 °C, 8 h; yield 42%. ^{1}H NMR (d_6-DMSO): 1.95 (s, 3 H, $CH_3(3')$); 1.2 (t, 3 H, $CH_2\underline{CH_3}$); 4.0 (q, 2 H, $\underline{CH_2}CH_3$); 2.3–2.5 (2 × s, 6 H, 2 CH_3); 4.5 (d, 1 H, H(5)); 4.8 (d, 1 H, H(6)); 3.28 (d, 2 H, $CH_2(3')$); 5.05 (d, 1 H, N−CO−NH); 5.5 (d, 2 H, $CH_2(2)$); 4.6 (s, 2 H, $\underline{CH_2}-C_6H_5$); 12.7 (s, 1 H, OH); 6.6–7.05 (2 × d, 5 H, C_6H_5-R). IR (KBr): 1645–1675 (amide I); 1510–1560 (amide II); 1760–1765 (β-lactam); 1245–1255 (C−O−C); 1380 (CH_3); 1685–1695 ($COOC_2H_5$); 2450–2800 (COOH); 3000–3100 (NH + OH).

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