7β-[2-(2-AMINOTHIAZOL-4-YL)-(*Z*)-2-METHOXYIMINOACETAMIDO]-3-[(1,2,3-THIADIAZOL-5-YL)THIOMETHYL]-CEPH-3-EM-4-CARBOXYLIC ACID A NEW POTENT CEPHALOSPORIN DERIVATIVE

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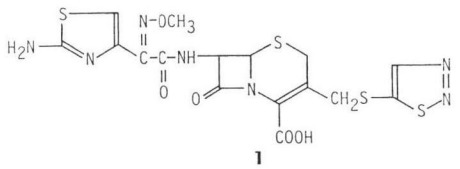
Recently several 7β-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]cephalosporins have appeared.* We report herein a new cephalosporin namely 7β-[2-(2-aminothiazol-4-yl)-(*Z*)-2-methoxyiminoacetamido]-3-[(1, 2, 3-thiadiazol-5-yl)-thiomethyl]ceph-3-em-4-carboxylic acid (**1**).

Compound **1** shows excellent activity against Gram-negative bacteria and has demonstrated uncharacteristically good activity against several Gram-positive organisms including *Staphylococcus aureus*. This information is illustrated in Table 1.



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The synthesis of compound **1** is illustrated on Chart 1. 2-(2-Tritylaminothiazol-4-yl)-(*Z*)-2-methoxyiminoacetic acid[2] was converted to the acid chloride **2** by treatment with phosphorus pentachloride. Condensation of compound **2** with the triethylammonium salt of 7-amino-3-[(1,2,3-thiadiazol-5-yl)thiomethyl]ceph-3-em-4-carboxylic acid[3]* (**3**) followed by acidification

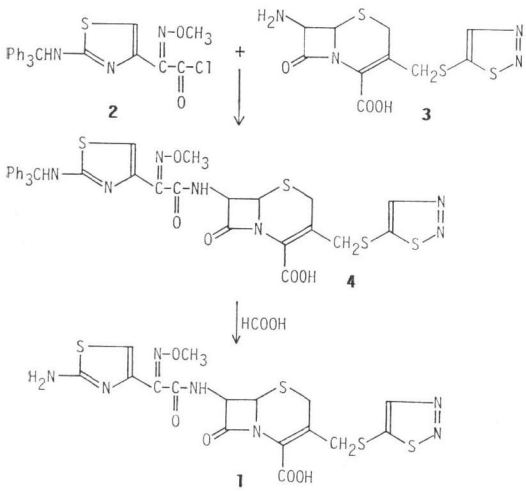
* For a recent review of this area see reference 1.

* New and improved syntheses of the 1,2,3-thiadiazole-5-thiol derivative necessary for the preparation of compound **3** will be reported elsewhere.

Table 1. *In vitro* activity of compound **1**.

Organism	Strain	MIC (μg/ml)
Staphylococcus aureus, β-lactamase negative	SSC–79–3	0.12
Staphylococcus aureus, β-lactamase negative	SSC–19–9	0.12
Staphylococcus aureus, β-lactamase positive	SSC–80–15	1
Staphylococcus aureus, β-lactamase positive	SSC–80–23	0.5
Streptococcus faecalis	SSC–81–3	32
Streptococcus β-hemolytic	K–71–5	≤0.015
Streptococcus pneumoniae	PMC–78–2	0.25
Streptococcus pneumoniae	PMC–78–5	0.25
Escherichia coli	K–81–12	0.12
Escherichia coli	SSC–80–75	0.06
Klebsiella pneumoniae	K–81–7	0.03
Klebsiella oxytoca	K–81–1	0.03
Enterobacter aerogenes	K–79–19	0.06
Enterobacter cloacae	SSC–80–69	0.25
Serratia marcescens	K–81–37	0.25
Serratia marcescens	TUL–78–17	0.25
Proteus morganii	K–79–25	0.06
Proteus vulgaris	K–77–2	0.25
Proteus inconstans	SSC–80–78	0.25
Salmonella sp.	SSC–79–57	0.25
Acinetobacter calcoaceticus	Stfd–79–17	32
Pseudomonas aeruginosa	UCLA–79–8	32
Bacteroides fragilis	NYC–77–8	16
Clostridium perfringens	NYC–77–11	0.5

Chart 1. Synthesis of compound **1**.



afforded the protected intermediate **4** which was readily converted to the desired product by formic acid treatment.

Experimental

7β-[2-(2-Tritylaminothiazol-4-yl)-(*Z*)-2-methoxyiminoacetamido]-3-[(1,2,3-thiadiazol-5-yl)-thiomethyl]ceph-3-em-4-carboxylic Acid

Phosphorus pentachloride (2.08 g) was added to an ice cold solution of 2-(2-tritylaminothiazol-4-yl)-(*Z*)-2-methoxyiminoacetic acid[2] (4.44 g) and triethylamine (1.41 ml) in 70 ml of methylene chloride. The mixture was stirred in the cold for 15 minutes, then evaporated to dryness. The residue was dissolved in a mixture of 50 ml of methylene chloride and 50 ml of acetone and again evaporated. Acetone (50 ml) was added to the residue and the mixture was filtered. The filtrate was chilled and added to an ice cold solution of 7-amino-3-[1, 2, 3-thiadiazol-5-yl)thiomethyl]ceph-3-em-4-carboxylic acid[3] (2.53 g) in 50 ml of acetone and 75 ml of water containing 0.84 g of sodium bicarbonate and 2.82 ml of triethylamine. The mixture was stirred in the cold for 0.5 hour, at room temperature for 1 hour and acidified to pH 2 with 4 N hydrochloric acid. Water (100 ml) was added and the mixture was extracted with three portions of ethyl acetate (150 ml each). The combined organic phase was washed twice with water then dried over magnesium sulfate. Evaporation gave 5.7 g of the product as a yellow glass. IR (KBr, cm^{-1}) 1785, 1715, 1685, 1515, 1040; NMR (DMSO-d_6) δ 3.82 (s, 3H), 4.25 (s, 2H), 5.20 (d, 1H, J=5Hz), 5.70 (dd, 1H, J=5 and 8 Hz), 6.73 (s, 1H), 7.33 (s, 15H), 8.80 (s, 1H), 8.90 (s, 1H), 9.60 (d, 1H).

7β-[2-(2-Aminothiazol-4-yl)-(*Z*)-2-methoxyiminoacetamido]-3-[(1, 2, 3-thiadiazol-5-yl)thiomethyl]ceph-3-em-4-carboxylic Acid

7β-[2-(2-Tritylaminothiazol-4-yl)-(*Z*)-2-methoxyiminoacetamido]-3-[(1,2,3-thiadiazol-5-yl)-thiomethyl]ceph-3-em-4-carboxylic acid (4.4 g) was added to 30 ml of 80% aqueous formic acid and stirred at room temperature for 2 hours. The mixture was filtered and the filtrate was treated with decolorizing charcoal and again filtered. The filtrate was evaporated to dryness at reduced pressure at 40°C and triturated in ether to form 2.4 g of the desired product as a white amorphous solid. IR (KBr, cm^{-1}), 1780, 1680, 1615, 1515, 1040; NMR (DMSO-d_6) δ 3.75, (pair of doublets, 2H, J=18 Hz, endocyclic $-CH_2S-$), 3.86 (s, 3H, OCH_3), 4.25 (s, 2H exocyclic $-CH_2S-$), 5.20 (d, 1H, J=5 Hz, 6H of 7ACA), 5.77 (dd, 1H, J=5 and 8 Hz, 7H of 7ACA), 6.75 (s, 1H, thiazole H), 7.20 (broad S, 2H, NH_2), 8.90 (s, 1H, thiadiazole H), 9.62 (d, 1H, J=8 Hz, –NH).

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