Synthesis and Antibacterial Properties of 7-[(2-Heteroarylthiazolo[3,2-*b*]-*s*-triazol-5-yl)acetamido]-cephalosporanic Acid Derivatives

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Received 18 September 1991

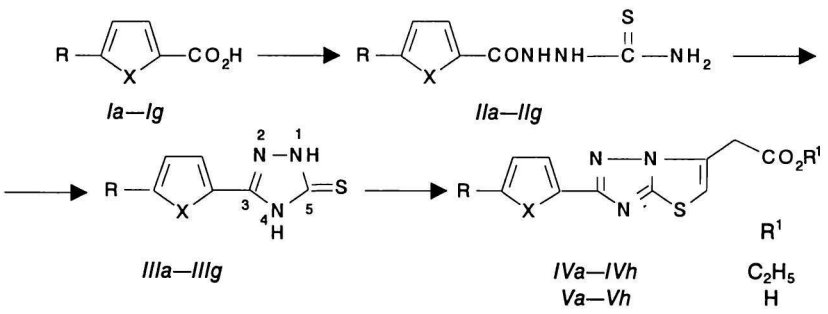
Series of 7-[(2-heteroarylthiazolo[3,2-*b*]-*s*-triazol-5-yl)acetamido]- and 7-{[2-(2-furyl)thiazolo[3,2-*b*]-*s*-triazol-5-yl]-2-methoxyiminoacetamido}cephalosporanic acids were prepared; both displayed better *in vitro* activity against gram-positive bacteria strains than against the gram-negative ones.

A great deal of highly antibacterially active broad-spectrum cephalosporin antibiotics possess the 2-aminothiazole grouping [1]. Further optimization of the acyl residue led to antibiotics of the (*Z*)-2-aminothiazol-4-yl-2-oxyimino derivatives [2]. Synthesis of derivatives with a fused 7-heteroarylacetamido substituent and the study of their biological activity have hitherto been only little reported [3]. A good antibacterial effect was found [4, 5] with cephalosporin derivatives containing furan or thiophene moiety. Therefore we investigated the influence of substitution on the thiazolo[3,2-*b*]-*s*-triazole moiety of the antibiotic.

The starting 1-acylthiosemicarbazides *IIa—IIg* were obtained by *N*-acylation of thiosemicarbazide [6] with chlorides of arenecarboxylic acids *Ia—Ig*. The subsequent cyclization gave the 3-heteroaryl-5-thioxo-1*H*,4*H*-*s*-triazoles *IIIa—IIIg*. The desired 2-heteroarylthiazolo[3,2-*b*]-*s*-triazol-5-ylacetic acids *V* were prepared by cyclization of triazoles *III* with ethyl 4-chloroacetoacetate in ethanol and base-catalyzed hydrolysis of esters *IVa—IVg* at room temperature in good yields (Scheme 1). Cyclization of the triazole *IIIc* was carried out in dimethylformamide and ethanol because of the low solubility of *IIIc* in ethanol and compound *VIc* was obtained. Derivative *IVc* was prepared by a long-term reflux of the triazole *IIIc* suspension with ethyl 4-chloroacetoacetate in ethanol. The hydrolysis has to be carried out at moderate conditions because that at reflux temperature of the ester *IVa* afforded the decarboxylation product 5-methyl-2-(2-furyl)thiazolo[3,2-*b*]-*s*-triazole. 2-(5-Nitro-2-furyl)thiazolo[3,2-*b*]-*s*-triazol-5-ylacetic acid (*Vh*) was prepared by acid hydrolysis of the corresponding ester *IVh* obtained by nitration of compound *IVa* with the nitration mixture of fuming nitric and sulfuric acids.

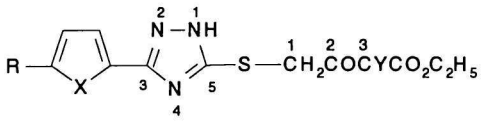
The model α-methoxyiminothiazolo[3,2-*b*]-*s*-triazoles *IX* could not be synthesized from triazoles *III* and ethyl (*Z*)-4-bromo-2-methoxyimino-3-oxobutyrate [7], because cyclization did not take place; instead, the *S*-alkylated acyclic derivatives *VIIa* and *VIIg* (Formula 1) were obtained. The cyclic derivative has not been prepared either by the change of reaction conditions (time, solvent, temperature), or by cyclization of the intermediates *VIIa*, *VIIg* by polyphosphoric acid.

The α-hydroxyimino ester *VIII* resulting from nitrosation of *IVa* was etherified with dimethyl sulfate in



	a	*b*	*c*	*d*	*e*	*f*	*g*	*h*
X	O	O	O	O	O	O	S	O
R	H	Ph	2-Cl—Ph	4-Cl—Ph	2,6-Cl_2—Ph	Br	H	NO_2

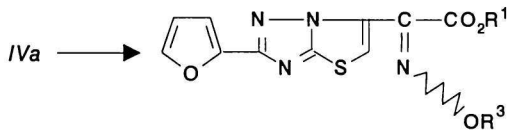
Scheme 1



	R	X	Y
VIc	2-Cl—Ph	O	H_2
VIIa	H	O	N—OCH_3
VIIg	H	S	N—OCH_3

Formula 1

the presence of potassium carbonate to afford the mixture of esters (*Z*)-*IX* and (*E*)-*IX* in the 3 : 1 ratio (as monitored by thin-layer chromatography). Arrangement of the methoxy group was deduced from spectral and physicochemical data: the H-6 signal of *VIII* was observed at δ = 7.99, a value close to that reported for the analogous *Z* isomer [8], the absorption band of the carbonyl group in the IR spectrum was split (indicative of the *Z* isomer [9]) and the reaction rate of base-catalyzed hydrolysis was different when compared with that of the *E* isomer; hydrolysis of the (*E*)-*IX* isomer proceeded with two equivalents of potassium hydroxide within 30 min at room temperature, to yield the corresponding acid (*E*)-*X* (Scheme 2). The (*Z*)-*IX* isomer did not undergo change at the same reaction conditions and the complete hydrolysis required five equivalents of potassium hydroxide and 3 h reaction time; application of these conditions to ester (*E*)-*IX* resulted in unidentified decomposition products.



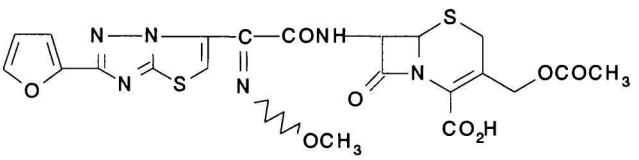
	R^1	R^3
(*Z*)-*VIII*	C_2H_5	H
(*Z*)-*IX*	C_2H_5	CH_3
(*E*)-*IX*	C_2H_5	CH_3
(*Z*)-*X*	H	CH_3
(*E*)-*X*	H	CH_3

Scheme 2

The synthetic approach to 7-[(2-heteroarylthiazolo-[3,2-*b*]-*s*-triazol-5-yl)acetamido]cephalosporanic acids is illustrated in Scheme 3. Chlorides of acids *Va—Vh*, obtained with phosphorus pentachloride under mild conditions were reacted without being isolated with silylated cephalosporanic intermediates *XI—XIV* generated *in situ* to afford the required 7-[(2-heteroarylthiazolo[3,2-*b*]-*s*-triazol-5-yl)acetamido]-substituted or unsubstituted 3-cephem-4-carboxylic acids *XIa—XIVg*.

Similarly, (*Z*)-2-(2-furyl)thiazolo[3,2-*b*]-*s*-triazol-5-yl-2-methoxyiminoacetic acid (*X*) furnished with silyl 7-aminocephalosporanate *XI via* its chloride, prepared with phosphorus pentachloride in dimethylacetamide and dichloromethane compound (*E*)-*XV* in high yield (Formula 2). The *E* conformation of *XV* was confirmed by position of the H-6 signal at δ = 8.51 [8, 10, 11]. The *Z* isomer *XV*, displaying the H-6 signal at δ = 7.98, was prepared similarly from the acid (*Z*)-*X* involving the Vilsmeier reagent.

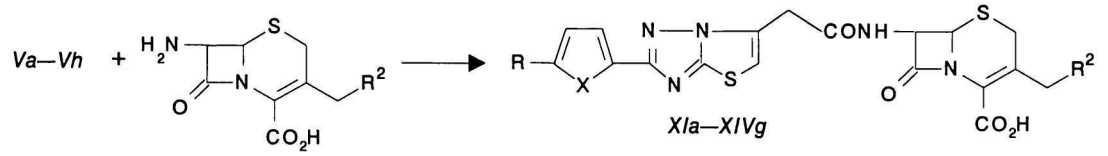
The IR spectra of triazole *VIc* revealed, in addition to characteristic absorptions of the aryl and



(*E*)-*XV*
(*Z*)-*XV*

Formula 2

heterocyclic moieties also stretching vibrations of two carbonyl groups at $\tilde{\nu}$ = 1690 and 1730 cm^{-1}, the *S*-alkylated derivatives *VIIa* and *VIIg* showed two bands of carbonyl and ethoxycarbonyl groups at $\tilde{\nu}$ = 1692, 1695 cm^{-1} and 1730, 1735 cm^{-1}, respectively.



	R^2		R^2
XI	$OCOCH_3$	*XIII*	MTZ
XII	H	*XIV*	MTD

MTZ – 1-methyl-1*H*-tetrazol-5-ylthio,
MTD – 2-methyl-1,3,4-thiadiazol-5-ylthio.

XIa—XIVg

	X	R		X	R
XIa	O	H	*XIIId*	O	4-Cl—Ph
XIIa	O	H	*XIe*	O	2,6-Cl_2—Ph
XIIIa	O	H	*XIIIe*	O	2,6-Cl_2—Ph
XIVa	O	H	*XIf*	O	Br
XIb	O	Ph	*XIIIf*	O	Br
XIIIb	O	Ph	*XIg*	S	H
XIVb	O	Ph	*XIIg*	S	H
XIc	O	2-Cl—Ph	*XIIIg*	S	H
XIIIc	O	2-Cl—Ph	*XIVg*	S	H
XId	O	4-Cl—Ph	*XIh*	O	NO_2
XIId	O	4-Cl—Ph	*XIIIh*	O	NO_2

Scheme 3

The ^{1}H NMR spectrum of compound *VIc* displayed the presence of two singlets of methylene groups and the amino proton at δ = 8.6.

In vitro tests of the antibacterial activity of compounds *XIa—XV* listed in Table 9 are relative to the standards. These compounds have the activity spectrum considerably different for gram-positive and gram-negative strains. Thus, *Bacillus subtilis*, *Bacillus cereus*, *Staphylococcus aureus* were inhibited by concentrations between 0.03 and 0.5 μg cm^{-3}. Noticeable was the activity decrease with 3-methylated analogues *XII* (minimum inhibitory concentration MIC 0.25 to 4 μg cm^{-3}). The effect against the common pathogen *Streptococcus pyogenes* was revealed at the concentration 0.125 to 1 μg cm^{-3}; this exceeds the activity of cephalosporin antibiotics of the first two generations. The activity against *Proteus sp.*, *Enterobacter cloacae*, and *Pseudomonas aeruginosa* strains was not detected, that against *Escherichia coli* and *Klepsiella pneumoniae* was similar or a little lower than with cefotaxime. Differences corresponding to one dilution step can be considered insignificant. The MIC values indicate that no potentiation of activity has taken place by introducing the condensed system and the excellent MIC values for gram-positive strains can be attributed to lipophilic heteroaryl substituents.

EXPERIMENTAL

Melting points were measured on a Kofler micro hot-stage, the IR spectra in KBr pellets and the UV spectra in methanol were determined with UV—VIS spectrophotometers, model 457 (Perkin—Elmer) and model 240 (Perkin—Elmer Hitachi), respectively. The ^{1}H NMR spectra of hexadeuterodimethyl sulfoxide solutions (unless otherwise stated) containing tetramethylsilane as internal reference were recorded with a spectrometer FX-100 (Jeol). The products were *in vitro* tested against gram-positive and gram-negative microorganisms (Czechoslovak Collection of Microorganisms, Masaryk University, Brno) by the dilution technique. The antibacterial activity was estimated as the minimum inhibitory concentration [12] (MIC, μg of the compound tested per 1 cm^3 of the nutrient). Thiosemicarbazide *IIa* and triazole *IIIa* were prepared according to [6].

1-Heteroarylthiosemicarbazides *IIb—IIg*

Solution of the respective heteroarenecarbonyl chloride (0.1 mol) in dry tetrahydrofuran (50 cm^3) was added to the suspension of thiosemicarbazide (9.1 g; 0.1 mol) in dry pyridine (100 cm^3) at −5 °C. The mixture was stirred for 12 h at room temperature, the solution was diluted with water (500 cm^3), pyridine was distilled off under reduced pressure and the oily residue was rubbed until crystalline. The crystals were filtered off, washed with water and ether and recrystallized from acetic acid. Characteristic data are listed in Table 1.

3-Heteroaryl-5-thioxo-1*H*,4*H*-*s*-triazoles *IIIb—IIIg*

1-Heteroarylthiosemicarbazide *II* (0.1 mol) refluxed in potassium hydroxide (10 %, 200 cm^3) for 6 h was left standing at room temperature for 16 h, acidified with glacial acetic acid to pH = 6.0 and the separated product was filtered off, washed with water, dried and crystallized from ethanol. Characteristic data are presented in Table 2.

Ethyl 2-Heteroarylthiazolo[3,2-*b*]-*s*-triazol-5-ylacetates *IVa—IVg*

The respective compound *III* (0.1 mol) in dry ethanol (400 cm^3) was refluxed for 8 h (*IIIe* for 18 h), the solvent was removed under diminished pressure and saturated aqueous sodium hydrogencarbonate was added to the residue. The separated product

Table 1. Characteristic Data of 1-Heteroarylthiosemicarbazides

Compound	Formula M_r	w_i(calc.)/% w_i(found)/% C	H	N	Yield/%	M.p./°C	$\tilde{\nu}$/cm^{-1} ν(C=O)
IIb	$C_{12}H_{11}N_3O_2S$	55.16	4.24	16.08	63	216—218	1680
	261.3	55.32	4.51	16.11			
IIc	$C_{12}H_{10}ClN_3O_2S$	48.73	3.41	14.21	54	215—217	1680
	295.7	49.02	3.40	14.24			
IId	$C_{12}H_{10}ClN_3O_2S$	48.73	3.41	14.21	51	223—225	1675
	295.7	48.64	3.49	14.18			
IIe	$C_{12}H_9Cl_2N_3O_2S$	43.65	2.75	12.72	40	208—210	1675
	330.2	43.64	2.85	12.72			
IIf	$C_6H_6BrN_3O_2S$	27.29	2.29	15.91	40	210—215	1665
	264.1	28.00	2.32	15.86			
IIg	$C_6H_7N_3OS_2$	35.80	3.51	20.88	61	191—193	1645
	201.3	35.62	3.42	21.16			

Table 2. Characteristic Data of 3-Heteroaryl-5-thioxo-1*H*,4*H*-*s*-triazoles

Compound	Formula M_r	w_i(calc.)/% w_i(found)/% C	H	N	Yield/%	M.p./°C	λ_{max}/nm log (ε/(m^2 mol^{-1}))
IIIb	$C_{12}H_9N_3OS$	59.24	3.71	17.27	83	254—256	317
	243.3	59.31	3.82	17.39			4.43
IIIc	$C_{12}H_8ClN_3OS$	51.89	2.90	15.13	85	265—267	316
	277.7	51.96	2.74	15.22			4.32
IIId	$C_{12}H_8ClN_3OS$	51.89	2.90	15.13	62	272—274	322
	277.7	51.74	3.11	15.17			4.47
IIIe	$C_{12}H_7Cl_2N_3OS$	46.17	2.26	13.46	87	139—141	296
	312.2	46.19	2.29	14.51			4.16
IIIf	$C_6H_4BrN_3OS$	29.28	1.64	17.07	65	218—221	290
	249.1	30.00	1.70	17.08			4.12
IIIg	$C_6H_5N_3S_2$	39.32	2.75	22.93	71	175—178	297
	183.2	38.82	3.01	23.11			4.01

was filtered off, washed with water and crystallized. Characteristic data are given in Tables 3 and 4.

Ethyl 2-(5-Nitro-2-furyl)thiazolo[3,2-*b*]-*s*-triazol-5-ylacetate (*IVh*)

Fuming nitric (4.5 cm^3) and sulfuric (17.9 cm^3) acids were introduced into the solution of compound *IVa* (19.4 g; 0.07 mol) in sulfuric acid (41 cm^3) at 15 °C. The mixture stirred at room temperature for 20 min was poured onto crushed ice, the separated crystals were filtered off, washed with water and recrystallized from ethanol.

Characteristic data are listed in Tables 3 and 4.

Decarboxylation of Substituted Ethyl *s*-Triazolylacetate *IVa*

Compound *IVa* (2.77 g; 10 mmol) was refluxed with sodium hydroxide (3 g) in ethanol (80 %, 80 cm^3) for 3.5 h. The solvent was distilled off under diminished pressure, the aqueous solution was acidified to pH = 2, the separated compound was filtered off, washed with water and crystallized from

Table 4. The ^{1}H NMR Chemical Shift Values (δ) for Ethyl 2-Heteroarylthiazolo[3,2-*b*]-*s*-triazol-5-ylacetates

Compound	CH_3CH_2 (Ester)	CH_2—CO	H-6	H_{arom} $H_{heteroarom}$
IVa	1.22 t, 4.20 q	4.13 s	7.43 s	6.68 dd, 7.05 d, 7.86 dd
IVb	1.24 t, 4.21 q	4.18 s	7.45 s	7.14—7.86 m
IVc	1.25 t, 4.18 q	4.20 s	7.45 s	7.42—7.95 m
				7.22 d, 7.35 d
IVd	1.20 t, 4.18 q	4.16 s	7.45 s	7.48—7.86 m
				7.15 d, 7.21 d
IVe	1.15 t, 4.15 q	4.15 s	7.42 s	7.47—7.73 m
				6.87 d, 7.25 d
IVf	1.22 t, 4.20 q	4.14 s	7.45 s	6.77 d, 7.07 d
IVg	1.19 t, 4.17 q	4.14 s	7.41 s	7.15 dd,
				7.66—7.71 m
IVh	1.22 t, 4.20 q	4.19 s	7.56 s	7.38 d, 7.85 d

Table 3. Characteristic Data of Ethyl 2-Heteroarylthiazolo[3,2-*b*]-*s*-triazol-5-ylacetates

Compound	Formula M_r	w_i(calc.)/% w_i(found)/% C	H	N	Yield/%	M.p./°C	$\tilde{\nu}$/cm^{-1}	λ_{max}/nm log (ε/(m^2 mol^{-1}))
IVa	$C_{12}H_{11}N_3O_3S$	51.98	3.99	15.15	77	91—93	1735	272
	277.3	52.08	3.94	15.17				4.40
IVb	$C_{18}H_{15}N_3O_3S$	61.18	4.28	11.89	77	139—141	1720	315
	353.4	61.22	4.24	11.87				4.59
IVc	$C_{18}H_{14}ClN_3O_3S$	55.74	3.64	10.83	40	133—135	1715	316
	387.8	55.70	3.67	10.79				4.59
IVd	$C_{18}H_{14}ClN_3O_3S$	55.74	3.64	10.83	76	114—116	1720	320
	387.8	55.90	3.70	10.86				4.61
IVe	$C_{18}H_{13}Cl_2N_3O_3S$	51.19	3.10	9.95	72	181—183	1718	282
	422.3	51.30	3.29	10.05				4.38
IVf	$C_{12}H_{10}BrN_3O_3S$	40.46	2.83	11.79	76	99—101	1720	280
	356.2	40.39	2.95	11.01				4.47
IVg	$C_{12}H_{11}N_3O_2S_2$	49.13	3.78	14.32	75	122—124	1722	281
	293.4	50.26	3.62	14.80				4.30
IVh	$C_{12}H_{10}N_4O_5S$	44.72	3.13	17.38	76	149—151	1725	339
	322.3	44.77	3.10	17.35				4.14

ethanol. Yield of compound 5-methyl-2-(2-furyl)-thiazolo[3,2-*b*]-*s*-triazole was 1.3 g (63 %), m.p. = 132—135 °C. For $C_9H_7N_3OS$ (M_r = 205.2) w_i(calc.): 52.67 % C, 3.44 % H, 20.47 % N; w_i(found): 52.81 % C, 3.62 % H, 20.53 % N. IR spectrum, $\tilde{\nu}$/cm^{-1}: 1615, 1435. ^{1}H NMR spectrum, δ: 3.70 (s, 3H, CH_3), 7.25 (s, 1H, H-6), 6.61—7.81 (m, 3H, $H_{heteroarom}$).

2-Heteroarylthiazolo[3,2-*b*]-*s*-triazol-5-ylacetic Acids *Va—Vg*

The above-mentioned compounds *IV* (0.1 mol) in methanol—tetrahydrofuran (φ_r = 1 : 1, 400 cm^3) were saponified with sodium hydroxide (10 %, 150 cm^3) at ambient temperature for 12 h. The organic solvents were distilled off under reduced pressure and the aqueous layer was extracted with ethyl acetate (50 cm^3). The aqueous phase was acidified with dilute hydrochloric acid, the separated product was filtered off, dried and crystallized from ethanol. Characteristic data are shown in Table 5.

2-(5-Nitro-2-furyl)thiazolo[3,2-*b*]-*s*-triazol-5-ylacetic Acid (*Vh*)

Concentrated hydrochloric acid (1.6 cm^3) was added to the solution of substance *IVh* (16.1 g; 50 mmol) in glacial acetic acid (160 cm^3). The mixture was refluxed for 24 h, evaporated to dryness, the residue was dissolved in saturated aqueous sodium hydrogencarbonate, extracted with ethyl acetate (30 cm^3), cooled to 0 °C and acidified with concentrated hydrochloric acid to pH = 1. The separated product was worked up and crystallized from ethanol. Characteristic data of acid *Vh* are presented in Table 5.

3-[5-(2-Chlorophenyl)-2-furyl]-5-(3-ethoxycarbonyl-2-oxopropylthio)-*s*-triazole (*VIc*)

Compound *IIIc* (2.78 g; 10 mmol) and ethyl 4-chloroacetoacetate (1.8 g; 11 mmol) were refluxed in ethanol—dimethylformamide (φ_r = 5 : 1, 60 cm^3) for 6 h. The solvent was evaporated to dryness *in vacuo* and the residue was chromatographed through a silica gel-packed column with dichloromethane—acetone (φ_r = 9 : 1) to give the *S*-alkyl derivative *VIc*. Yield 1.4 g (35 %, light petroleum), m.p. = 101—103 °C. For $C_{18}H_{16}ClN_3O_4S$ (M_r = 405.8) w_i(calc.): 53.26 % C, 3.97 % H, 10.35 % N; w_i(found): 53.09 % C, 3.99 % H, 10.15 % N. UV spectrum, λ/nm (log {ε}): 316 (4.53). IR spectrum, $\tilde{\nu}_{max}$/cm^{-1}: 1690, 1730. ^{1}H NMR spectrum, δ: 1.21 (t, 3H, CH_3), 3.88 (s, 2H, CH_2), 4.17 (q, 2H, CH_2), 4.35 (s, 2H, CH_2), 7.21—7.65 (m, 4H, H_{arom}).

3-(2-Furyl)- resp. 3-(2-Thienyl)-5-(3-ethoxycarbonyl-2-oxo-3-methoxyiminopropylthio)-*s*-triazole (*VIIa* resp. *VIIg*)

Compound *IIIa* (0.83 g; 5 mmol) resp. *IIIg* (1.03 g; 10 mmol) and ethyl 4-bromo-2-methoxyimino-3-oxobutyrate (1.3 g; 5 mmol) were refluxed in ethanol (25 cm^3) for 3 h. Saturated aqueous sodium hydrogencarbonate was added to the cooled mixture and ethanol was distilled off under reduced pressure. The separated compound was filtered off and crystallized from chloroform—ether to afford the *S*-alkyl derivative.

VIIa; yield 1.0 g (59 %), m.p. = 105—107 °C. For $C_{13}H_{14}N_4O_5S$ (M_r = 338.3) w_i(calc.): 46.15 % C, 4.17 % H, 16.56 % N; w_i(found): 46.19 % C, 4.21 % H, 16.63 % N. UV spectrum, λ/nm (log {ε}): 245 (4.25).

Table 5. Characteristic Data of 2-Heteroarylthiazolo[3,2-*b*]-*s*-triazol-5-ylacetic Acids

Compound	Formula	w_i(calc.)/% w_i(found)/%			Yield/%	M.p./°C	$\tilde{\nu}$/cm^{-1}
	M_r	C	H	N			ν(C=O)
Va	$C_{10}H_7N_3O_3S$	48.19	2.83	16.86	86	251—252	1710
	249.2	48.36	2.88	16.83			
Vb	$C_{16}H_{11}N_3O_3S$	59.07	3.41	12.91	71	291—292	1710
	325.3	59.19	3.43	12.86			
Vc	$C_{16}H_{10}ClN_3O_3S$	53.41	2.80	11.68	81	305—306	1710
	359.8	53.62	2.91	11.75			
Vd	$C_{16}H_{10}ClN_3O_3S$	53.41	2.80	11.68	72	292—294	1708
	359.8	53.28	2.85	11.75			
Ve	$C_{16}H_9Cl_2N_3O_3S$	48.75	2.30	10.66	50	252—253	1710
	394.2	48.91	2.42	10.11			
Vf	$C_{10}H_6BrN_3O_3S$	36.60	1.84	12.81	65	231—234	1715
	328.2	36.48	1.92	12.76			
Vg	$C_{10}H_7N_3O_2S_2$	45.27	2.66	15.84	79	220—222	1710
	265.3	45.39	2.72	15.86			
Vh	$C_{10}H_6N_4O_5S$	40.82	2.06	19.04	82	245—247	1700
	294.2	40.67	1.71	18.59			

IR spectrum, $\tilde{\nu}_{max}/cm^{-1}$: 1692, 1738. ^1H NMR spectrum, δ: 1.24 (t, 3H, CH_3), 4.13 (s, 3H, OCH_3), 4.29 (q, 2H, OCH_2), 4.63 (s, 2H, CH_2), 10.78 (br s, 1H, NH).

VIIg; yield of the bromide 2.3 g (53 %), m.p. = 162—174 °C. IR spectrum, $\tilde{\nu}_{max}/cm^{-1}$: 1695, 1735. ^1H NMR spectrum, δ: 1.23 (t, 3H, CH_3), 4.12 (s, 3H, OCH_3), 4.32 (q, 2H, OCH_2), 4.58 (s, 2H, CH_2).

Ethyl [2-(2-Furyl)thiazolo[3,2-*b*]-*s*-triazol-5-yl]-hydroxyiminoacetate (*VIII*)

Isopentyl nitrite (12.9 g; 0.11 mol) was dripped into the solution of compound *IVa* (27.7 g; 0.1 mol) and sodium ethoxide (7.48 g; 0.11 mol) in dry ethanol (700 cm^3) at −10 °C. The mixture was stirred at room temperature for 12 h, ethanol was removed *in vacuo* and the remaining solid was treated with water (200 cm^3). The solution was acidified with hydrochloric acid, the product was filtered off and crystallized from ethyl acetate. Characteristic data are given in Tables 6 and 7.

Ethyl (*Z*)- and (*E*)-[2-(2-Furyl)thiazolo[3,2-*b*]-*s*-triazol-5-yl]methoxyiminoacetates (*IX*)

Dimethyl sulfate (1.33 g; 10.5 mmol) was added to a well stirred mixture composed of compound *VIII* (3.06 g; 10 mmol) and potassium carbonate (2.3 g) in acetone (90 cm^3) at 15 °C. The mixture was stirred for 7 h, poured into water and extracted with ethyl acetate (3 × 70 cm^3). The oily product, obtained by evaporation of the organic layer, was chromatographed through a silica gel-packed column with benzene—ethyl acetate (φ_r = 5 : 1) to afford (*Z*)-*IX* as the first eluate in 60 % yield (1.9 g, crystallized from benzene—petrol). The *E* isomer *IX* (0.4 g, 13 %) was present in the second fraction. This product was crystallized from petrol. Characteristic data are listed in Tables 6 and 7.

(*Z*)- and (*E*)-[2-(2-Furyl)thiazolo[3,2-*b*]-*s*-triazol-5-yl]methoxyiminoacetic Acid (*X*)

(*Z*)-*IX* (1 g; 31 mmol) resp. (*E*)-*IX* (10 mmol) was hydrolyzed with potassium hydroxide (0.87 g; 150 mmol resp. 20 mmol) in ethanol (80 %, 35 cm^3) at room temperature for 3 h. The solvent was distilled off under diminished pressure and the aqueous solution was acidified to pH = 1.5. The product was filtered off and crystallized from ethanol. Yield 0.6 g (67 %) resp. 0.2 g (69 %). Characteristic data are given in Tables 6 and 7.

7-[(2-Heteroarylthiazolo[3,2-*b*]-*s*-triazol-5-yl)acetamido]-3-(heteroarylthiomethyl)-, -3-(Acetoxymethyl)- resp. -3-Methyl-3-cephem-4-carboxylic Acids *XIa—XIVg* and (*E*)-7-{[2-(2-Furyl)thiazolo-[3,2-*b*]-*s*-triazol-5-yl]-2-methoxyiminoacetamido}-cephalosporanic Acid ((*E*)-*XV*)

Phosphorus pentachloride (2.8 mmol) was poured into the solution of the respective acids *Va—Vh*, (*Z*)-*X* (2 mmol) in dimethylacetamide (20 mmol) and dichloromethane (15 cm^3) at 5 °C. The mixture was stirred till clear and cooled to −10 °C. A solution containing 7-amino-3-(acetoxymethyl)- (*XI*), or -3-

Table 6. Characteristic Data of [2-(2-Furyl)thiazolo[3,2-*b*]-*s*-triazol-5-yl]oxyiminoacetates

Compound	Formula M_r	w_i(calc.)/% w_i(found)/% C	H	N	Yield/%	M.p./°C	$\tilde{\nu}/cm^{-1}$ ν(C=O)
VIII	$C_{12}H_{10}N_4O_4S$	47.05	3.29	18.29	56	183—186	1710
	306.3	47.28	3.61	18.35			
(*Z*)-*IX*	$C_{13}H_{12}N_4O_4S$	48.74	3.78	17.49	60	83—85	1745
	320.3	48.79	3.81	17.59			
(*E*)-*IX*	$C_{13}H_{12}N_4O_4S$	48.74	3.78	17.49	20	133—135	1728
	320.3	48.52	3.71	17.56			
(*Z*)-*X*	$C_{11}H_8N_4O_4S$	45.21	2.76	19.17	82	215—217	1720
	292.3	45.32	2.68	19.19			
(*E*)-*X*	$C_{11}H_8N_4O_4S$	45.21	2.76	19.17	31	174—176	1720
	292.3	45.32	2.79	19.19			

Table 7. The ^1H NMR Chemical Shift Values (δ) for [2-(2-Furyl)thiazolo[3,2-*b*]-*s*-triazol-5-yl]oxyiminoacetates

Compound	CH_3CH_2 (Ester)	CH_3 (Oxime)	H-6	$H_{heteroaryl}$
VIII	1.26 t 4.33 q	–	7.99 s	6.68 dd, 7.05 d, 7.88 d
(*Z*)-*IX*	1.27 t 4.35 q	4.14 s	8.07 s	6.68 dd, 7.06 dd, 7.88 dd
(*Z*)-*X*	– –	3.88 s	7.55 s	6.68 dd, 7.05 d, 7.83 s
(*E*)-*IX*	1.30 t 4.41 q	4.16 s	8.61 s	6.68 dd, 7.45 dd, 7.88 d
(*E*)-*X*	– –	3.84 s	8.48 s	6.69 dd, 7.06 d, 7.88 d

(heteroarylthiomethyl)- (*XIII*, *XIV*), or -3-methyl-3-cephem-4-carboxylic acid (*XII*) (2 mmol) and *N*,*O*-bis(trimethylsilyl)acetamide (6 mmol) in dichloromethane (15 cm^3) was added to the cooled solution and stirred at −10 °C for 30 min and at ambient temperature for 2 h. Dichloromethane was removed *in vacuo* and saturated sodium hydrogencarbonate solution (20 cm^3) was added to the residue. This solution was extracted with ethyl acetate (2 × 10 cm^3), the aqueous layer was acidified with hydrochloric acid (15 %) to pH = 2. The separated product was extracted with ethyl acetate (3 × 10 cm^3) and the combined extracts were washed with water, dried over magnesium sulfate and the solvent was distilled off. Ether (30 cm^3) was added to the solid residue with vigorous stirring and the crystal-

Table 8. Characteristic Data of 7-[(2-Heteroarylthiazolo[3,2-*b*]-*s*-triazol-5-yl)acetamido]cephalosporanic Acids

Compound	Formula	w_i(calc.)/%			Yield/%	M.p./°C	$\tilde{\nu}$/cm^{-1}	λ_{max}/nm
	M_r	w_i(found)/%					ν(C=O)	log (ε/(m^2 mol^{-1}))
		C	H	N				
XIa	$C_{20}H_{17}N_5O_7S_2$	47.71	3.40	13.91	45	152—153	1770	270
	503.5	47.82	3.51	13.87				4.40
XIb	$C_{26}H_{21}N_5O_7S_2$	53.88	3.65	12.08	52	169—171	1772	316
	579.6	53.79	3.62	12.00				4.12
XIc	$C_{26}H_{20}ClN_5O_7S_2$	50.86	3.28	11.14	42	168—172	1770	316
	614.1	50.72	3.33	11.11				–
XId	$C_{26}H_{20}ClN_5O_7S_2$	50.86	3.28	11.14	40	162—164	1778	320
	614.1	50.92	3.39	11.28				4.53
XIe	$C_{26}H_{19}Cl_2N_5O_7S_2$	48.16	2.95	10.80	62	138—140	1778	267
	648.5	48.25	2.87	11.12				–
XIf	$C_{20}H_{16}BrN_5O_7S_2$	41.25	2.77	12.02	63	162—165	1775	275
	582.4	41.32	2.83	12.15				4.44
XIg	$C_{20}H_{17}N_5O_6S_3$	46.23	3.30	13.48	57	141—144	1775	276
	519.6	46.36	3.28	13.56				–
XIh	$C_{20}H_{16}N_6O_9S_2$	43.71	2.94	15.30	48	189—192	1770	242
	548.5	43.98	2.86	15.45				4.18
XIIa	$C_{18}H_{15}N_5O_5S_2$	48.53	3.39	15.72	36	160—164	1775	268
	445.5	48.61	3.41	15.62				4.45
XIId	$C_{24}H_{18}ClN_5O_5S_2$	51.84	3.26	12.60	33	158—162	1776	265
	556.0	51.79	3.72	12.42				–
XIIg	$C_{18}H_{15}N_5O_4S_3$	46.84	3.28	15.17	30	163—166	1776	277
	461.5	47.01	3.27	15.29				–
XIIIa	$C_{20}H_{17}N_9O_5S_3$	42.92	3.06	22.53	45	106—109	1775	272
	559.6	43.02	2.89	22.42				4.50
XIIIb	$C_{26}H_{21}N_9O_5S_3$	49.12	3.33	19.83	49	176—179	1765	–
	635.7	49.15	3.42	19.79				–
XIIIc	$C_{26}H_{20}ClN_9O_5S_3$	46.60	3.01	18.81	37	160—165	1775	–
	670.1	46.87	2.93	19.11				–
XIIId	$C_{26}H_{20}ClN_9O_5S_3$	46.59	3.01	18.81	48	167—170	1778	–
	670.1	46.63	3.10	18.76				–
XIIIe	$C_{26}H_{19}Cl_2N_9O_5S_3$	44.32	2.72	17.89	75	172—175	1774	–
	704.5	44.28	2.69	17.71				–
XIIIf	$C_{20}H_{16}BrN_9O_5S_3$	37.62	2.52	19.70	56	136—139	1772	274
	638.5	37.54	2.61	19.69				–
XIIIg	$C_{20}H_{17}N_9O_4S_4$	41.73	2.98	21.90	5	171—174	1765	276
	575.7	41.82	3.15	21.78				4.36
XIIIh	$C_{20}H_{16}N_{10}O_7S_3$	39.73	2.67	23.17	48	171—174	1775	–
	604.6	39.69	2.65	22.87				–
XIVa	$C_{21}H_{17}N_7O_5S_4$	43.81	2.98	17.00	43	121—124	1768	272
	575.6	44.01	2.77	17.11				4.53
XIVb	$C_{27}H_{21}N_7O_5S_4$	49.75	3.25	15.04	37	139—142	1778	315
	651.7	49.29	3.27	15.08				4.51
XIVg	$C_{21}H_{17}N_7O_4S_5$	42.62	2.88	16.58	5	171—174	1765	276
	591.6	44.05	3.11	17.05				4.36
(*E*)-*XV*	$C_{21}H_{18}N_6O_8S_2$[a]	46.15	3.32	15.38	72	164—167	1775	266
	546.5	44.71	3.58	15.89				4.01
(*Z*)-*XV*	$C_{21}H_{18}N_6O_8S_2$[b]	46.15	3.32	15.38	21	162—165	1775	266
	546.5	45.18	3.52	17.83				4.09

The ^{1}H NMR chemical shift values (δ) (hexadeuterodimethyl sulfoxide/tetramethylsilane): *a*) 4.03 (s, 3H, OCH_3), 8.51 (s, 1H, H-6), 9.30 (d, 1H, CONH); *b*) 4.08 (s, 3H, OCH_3), 7.98 (s, 1H, H-6), 9.55 (d, 1H, CONH).

Table 9. *In vitro* Antibacterial Activity of 7-[(2-Heteroarylthiazolo[3,2-*b*]-*s*-triazol-5-yl)acetamido]cephalosporanic Acids

Compound	MIC/(μg cm^{-3})					
	B. subtilis CCM 1999	*B. cereus* CCM 869	*S. aureus* IEM Mau 78/71	*S. pyogenes* IEM A1/49	*E. coli* IEM Eck 67/59	*K. pneumoniae* CCM 1848
XIa	0.125	–	0.125	0.25	0.5	128
XIIa	4	4	4	4	4	2
XIIIa	0.25	0.5	0.5	0.5	1	0.5
XIVa	0.125	–	0.125	0.25	0.25	0.5
XIb	0.125	–	0.25	0.25	0.25	128
XIIIb	0.125	0.125	0.25	1	0.06	–
XIVb	0.125	–	0.125	0.125	0.125	0.125
XId	0.125	–	0.25	1	1	32
XIId	4	4	1	2	–	128
XIIId	0.125	0.125	0.125	0.125	0.125	0.125
XIe	0.125	–	0.125	0.125	0.25	32
XIIIe	2	4	4	16	2	–
XIf	0.25	–	128	–	1	32
XIIIf	0.25	0.5	0.25	0.25	0.5	0.5
XIg	0.125	–	0.125	1	0.5	32
XIIg	4	4	–	–	0.5	128
XIIIg	0.125	–	0.125	0.125	0.25	0.125
XIVg	0.125	0.125	0.125	0.25	0.125	0.125
XIh	0.25	0.25	0.125	0.5	0.25	0.125
XIIIh	0.5	0.5	0.5	4	0.25	–
(*E*)-*XV*	128	128	8	128	64	16
(*Z*)-*XV*	0.125	0.125	0.125	128	0.125	–
CFX	0.125	–	0.125	0.125	0.125	0.5
CZL	0.125	0.125	0.5	128	1	–

CFX = cefotaxime, CZL = cefazolin.

line product was filtered off, dissolved in ethanol at 40 °C and crystallized by addition of ether. The product was filtered off and washed with ether. Characteristic data are presented in Table 8, antibacterial activity is given in Table 9.

(*Z*)-7-{[2-(2-Furyl)thiazolo[3,2-*b*]-*s*-triazol-5-yl]-2-methoxyiminoacetamido}cephalosporanic Acid ((*Z*)-*XV*)

The acid (*Z*)-*X* (2.1 g; 7 mmol) and *N*-methylmorpholine (0.78 g; 7.7 mmol) were added at – 5 °C to oxalyl chloride (0.88 g; 7 mmol) and dimethylformamide (0.5 g; 7 mmol) dissolved in dichloromethane (20 cm^3). The mixture was stirred at – 5 °C for 30 min; a solution of 7-aminocephalosporanic acid (1.9 g; 7 mmol) and *N*,*O*-bis(trimethylsilyl)-acetamide (5.7 g; 20 mmol) in ethyl acetate (20 cm^3), obtained by a 20 min reflux, was gradually added into the previous slightly turbid solution. The mixture was then stirred at – 5 °C and 20 °C for 3 h and 1 h, respectively, and alkalized with cooling with saturated aqueous sodium hydrogencarbonate (30 cm^3). The aqueous layer was acidified with hydrochloric acid (φ_r = 1 : 3) and extracted with ethyl acetate (20 cm^3). The extract was decolourized with charcoal and concentrated to one third of its original volume; a stepwise addition of ether (30 cm^3) brought about the crystallization. Yield 0.8 g (21 %), m.p. = 162—165 °C. Further data are listed in Table 8.

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Translated by Z. Votický