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Synthetic β-Lactam Antibiotics IV. Antibacterial activity of some 7β-[2-(2-Aminothiazol-4-yl)-2-(methoxyimino) acetamido]-3-(1-alkyl-1H-tetrazol-5-yl)thiomethyl-cephalosporins

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3-[(1-Methyl-1H-tetrazol-5-yl)thiomethyl] is one of the most important side chains in cephalosporins. This side chain which occurs in numerous antibacterial agents, such as cefamandole, latamoxef, cefoperazone, and cefmenoxime, contributes remarkable potency and broad spectrum[1]. For the continuous work of study on the development of broad spectrum cephalosporins, we became interested in the effect of structural modification of the substituent at the N-1 position of mercaptotetrazole toward biological activity because our recent work had demonstrated that the arylsubstituted mercaptotetrazoles (Fig. 1) had favorable effect on the activity against Gram-positive bacteria[2].

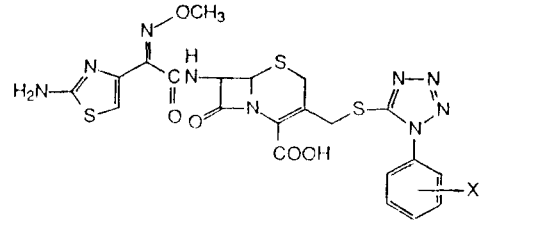
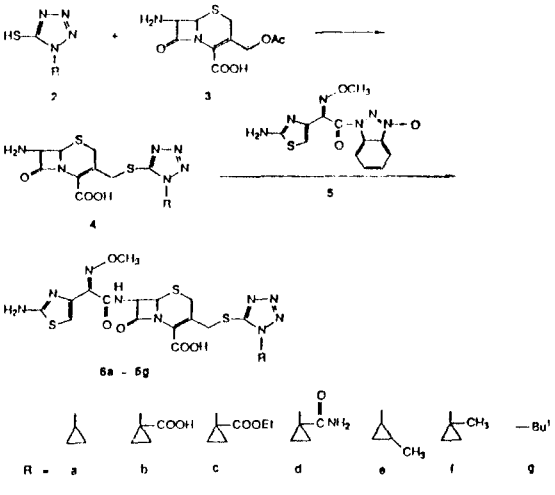


Fig. 1. Structure 1

The main focus of this report was to investigate the relationship between activity and functional groups in the mercaptotetrazole.

The compounds **6a-6g** tested were prepared as shown in Scheme 1. The mercaptotetrazoles **2a-2g** from the corresponding amines and the tetrazolthiomethyl-cephalosporanic acid **4a-4g** were prepared by the previously reported methods[3-5]. Reaction between compounds **4** and **5** in 5% aqueous acetone in the presence of triethylamine to yield cephalosporins **6a-6g** in satisfactory yields[2]. The NMR spectral data of compounds **6a-6g** were shown in Table I.



Scheme 1.

The *in vitro* antibacterial activity of compounds **6a-6g** was determined by the standard two fold agar dilution method. The result are given as MIC (μg/ml) in Table II in comparison with those of cefotaxime and cefoperazone. As indicated in the table, compound **6a-6g** have potent activity with widely expanded spectra against most Gram-positive and Gram-negative organisms. Against Gram-positive bacteria, the activity of compounds **6c**, **6e**, **6f**, and **6g** was comparable to that of cefotaxime. Against Gram-negative bacteria, compounds **6d** and **6g** displayed potent activity comparable or slightly inferior to that of cefotaxime. In fact, the compound **6f** showed much better activity than cefotaxime against *Streptococcus pyogenes* 308, *Streptococcus faecium* MD **8b**, and *Escherichia coli* DC 2. Except pseudomonal activity, compounds **6c**, **6e** and **6f** showed comparable activity or superior to that of cefoperazone against many organisms.

It is interesting note that compounds such as **6e**, **6f** and **6g** with lipophilic functions in the tetrazole exhibited increase of the activity against Gram-positive

Table I. NMR spectral data of cephalosporins

Compound No.	^{1}H NMR value (DMSO-d_6) 2-CH_2 (2H, ABg J = 18 Hz)	3-CH_2 (2H, ABg)	6-H (1H, d d J = 5 Hz)	7-H (1H, dd)	O C H N (1H, d J = 8 Hz)	OCH_3 (3H, s)	Thiazole (1H, s)	R
6a	3.67	4.41	5.04	5.63	9.59	3.84	6.73	4.03 (1H, m) 0.65 – 1.28 (4H, m)
6b	3.68	4.45	5.13	5.78	9.62	3.84	6.74	1.79 (4H, d)
6c	3.82	4.44	5.16	5.80	9.73	3.89	6.82	4.14 (2H, q) 1.90 (4H, m) 1.15 (3H, t)
6d	3.71	4.43	5.12	5.78	9.64	3.84	6.76	1.78 (s, 2H) 1.56 (s, 2H)
6e	3.80	4.47	5.22	5.87	9.73	3.93	6.85	3.44 (1H, m) 0.86 – 1.70 (6H, m)
6f	3.47	4.32	5.00	5.58	9.49	3.76	6.37	1.37 (3H, s) 1.03 – 1.16 (4H, m)
6g	3.80	4.52	5.19	5.84	9.68	3.90	6.82	1.70 (9H, s)

Table II. *In vitro* antibacterial activity (MIC, g/m*l* of cephalosporins

Organism	**6a**	**6b**	**6c**	**6d**	**6e**	**6f**	**6g**	Cefotaxime	Cefoperazone
Streptococcus pyogenes 308	0.013	0.025	0.004	0.007	0.007	<0.002	0.004	0.007	0.098
Streptococcus pyogenes 77	ND	0.007	<0.002	0.007	0.004	<0.002	<0.002	<0.002	0.049
Streptococcus faecium MD 8b	12.5	>100	>100	>100	100	6.25	>100	100	6.25
Straphylococcus aureus SG 511	3.125	6.25	1.563	6.25	1.563	1.563	1.563	1.563	1.563
Straphylococcus aureus 285	3.125	6.25	1.563	6.25	1.563	1.563	1.563	1.563	1.563
Straphylococcus aureus 503	1.563	6.25	1.563	3.125	0.781	0.781	0.781	0.781	1.563
Escherichia coli O 55	0.098	0.195	0.195	0.025	0.049	0.049	0.098	0.007	0.125
Escherichia coli DC 0	0.391	0.391	0.781	0.098	0.195	0.195	0.195	0.013	0.049
Escherichia coli DC 2	0.025	0.098	0.025	0.025	0.013	<0.002	0.013	0.007	0.025
Escherichia coli TEM	0.195	0.195	0.781	0.098	0.195	0.195	0.195	0.025	1.563
Escherichia coli 1507E	0.391	0.391	0.781	0.098	0.391	0.195	0.391	0.025	0.098
Pseudomonas aeruginosa 9027	50	25	50	50	50	25	100	12.5	3.125
Pseudomonas aeruginosa 1592E	50	25	50	50	50	25	100	12.5	6.25
Pseudomonas aeruginosa 1771	25	3.125	0.195	12.5	12.5	12.5	25	6.25	3.125
Pseudomonas aeruginosa 1771M	0.781	0.391	0.195	0.195	0.098	0.195	0.195	0.049	0.195
Salmonella typhimirium	0.098	0.391	0.195	0.098	0.195	0.098	0.781	0.025	0.195
Klebsiella oxytoca 1082E	6.25	12.5	6.25	25	3.125	3.125	6.25	0.781	>100
Klebsiella aerogenes 1522 E	0.195	0.098	0.391	0.049	0.195	0.195	0.391	0.013	0.049
Enterobacter cloacae P 99	>100	>100	>100	>100	>100	>100	>100	>100	>100
Enterobacter cloacae 1321E	0.098	0.049	0.098	0.013	0.098	0.098	0.098	0.004	0.007

bacteria and the compound **6b** with hydrophilic function showed increase of the activity against *Pseudomonas aeruginosa*. But the result indicates that influence of the substituent of mercaptotetrazole on activity was not solely dependent on the nature of their functional groups.

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