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NOTES

New Cephalosporin Antibiotics with 3-Triazolylpyridiniummethyl Substituents

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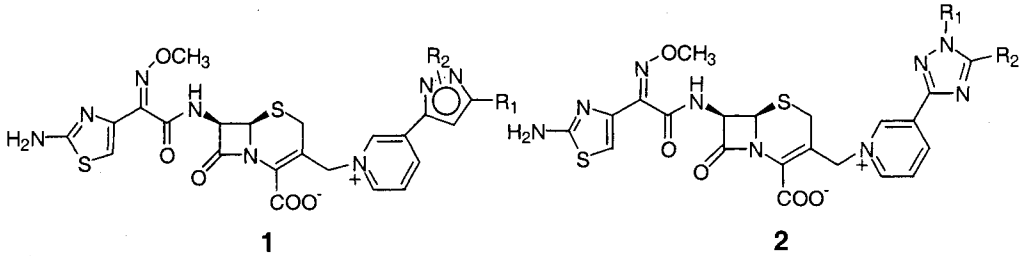
In the preceding paper,[1] we reported the synthesis of a novel series of cephalosporins **1** having a 3-(pyrazol-3-yl)pyridinium group at the C-3′ position (Fig. 1) and have described their antimicrobial activity against Gram-positive and Gram-negative bacteria. There we introduced a 3-(pyrazol-3-yl)pyridinium group at the C-3′ position as a combination of the pyridine moiety of ceftazidime[2] and the pyrazole moiety of cefoselis[3] to attain a synergic effect in activity. As we expected, those compounds exhibited well-balanced and broad spectrum of activity against Gram-positive and Gram-negative bacteria. Of them, 7-[(*Z*)-2-(2-amino-1,3-thiazol-4-yl)-2-(methoxyimino)acetamido]-3-[(3-(5-amino-pyrazol-3-yl)pyridinium)methyl]-3-cephem-4-carboxylic acid (**1a**)[1] showed the best activity comparable to cefpirome,[4] and the SAR study showed that the amine functionality at the 5-position of the pyrazole ring was crucial for the activity. These results have encouraged us to introduce another heterocyclic component, triazole, in place of pyrazole to see its effect on activity. In this paper, we wish to describe the synthesis of a new series of quaternary ammonium cephalosporins **2** with 3-triazolylpyridiniummethyl derivatives and the effect of substituents on the triazole ring on their activity (Fig. 1).

The preparation of various 3-(triazol-3-yl)pyridine derivatives, the substituents at the C-3′ position, was accomplished following known procedures.[5~8]

The cephalosporin derivatives **2** were prepared according to the general procedure described in the previous paper (Scheme 1).[1] [**2d** (R_1=CH_3, R_2=H): mp 215~217°C (dec); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.14~3.52 (2H, ABq, J=17.5 Hz, C_4-H), 3.77 (3H, s, OCH_3), 4.0 (3H, s, triazole-NCH_3), 5.06 (1H, d, J=4.8 Hz, C_6-H), 5.24~5.79 (2H, ABq, J=14.5 Hz, C_3–CH_2–), 5.64 (1H, d, J=4.8 Hz, C_7-H), 6.7 (1H, s, thiazole-H), 7.19 (2H, br s, thiazole-NH_2), 8.24 (1H, dd, J=6.1 Hz, J=8.2 Hz, pyridine-H), 8.76 (1H, s, triazole-H), 8.98 (1H, d, J=8.2 Hz, pyridine-H), 9.53 (1H, d, J=8.2 Hz, pyridine-H), 9.58 (1H, d, J=6.1 Hz, pyridine-H), 9.96 (1H, br s, –CONH–).]

The *in vitro* activity (MIC) of the new cephalosporins

Fig. 1. General structures of 3-heterocyclylpyridiniummethylcephalosporins.



1

R_1 = H, CH_3, NH_2, CH_2OH, $CONH_2$
R_2 = H, CH_3, CH_2CH_2OH
(**1a** : R_1 = NH_2, R_2 = H)

2

R_1 = H, CH_3, CH_2CH_2OH
R_2 = H, CH_3, SMe, OH, NH_2

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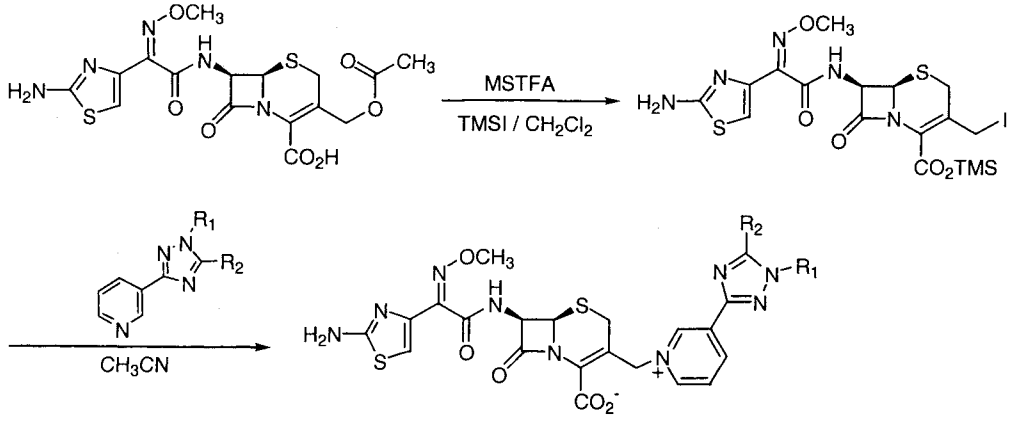
Scheme 1. Synthesis of 3-(triazol-3-yl)pyridiniummethylcephalosporins.



	2a	2b	2c	2d	2e	2f	2g	2h	2i	2j
R_1	H	H	H	CH_3	CH_3	CH_3	NH_2	CH_2CH_2OH	CH_2CH_2OH	CH_2CH_2OH
R_2	H	NH_2	SMe	H	CH_3	NH_2	OH	H	CH_3	NH_2

Table 1. *In vitro* antimicrobial activity of the cephalosporins **2a**~**j** (MIC: μg/ml).

Strains	Compounds												
	CPR	CAZ	**1a**	**2a**	**2b**	**2c**	**2d**	**2e**	**2f**	**2g**	**2h**	**2i**	**2j**
S.p. 308	0.007	0.098	0.007	0.007	0.013	0.013	0.013	0.013	0.025	0.781	0.013	0.013	0.025
S.p. 77A	0.007	0.049	0.007	0.007	0.025	0.049	0.025	0.025	0.025	0.781	0.049	0.048	0.025
S.p. SG 511	0.781	12.5	0.781	1.563	3.125	3.125	3.125	6.25	3.125	>100	6.25	3.125	3.125
S.a. 285	0.781	12.5	0.781	0.781	3.125	6.25	6.25	6.25	6.25	>100	6.25	6.25	3.125
S.a. 503	0.195	3.125	0.391	0.781	0.781	1.563	1.563	3.125	1.563	100	3.125	1.563	1.563
E.c. 055	0.025	0.098	0.013	0.025	0.049	0.098	0.098	0.098	0.195	1.563	0.098	0.098	0.098
E.c. DC 0	0.013	0.098	0.025	0.013	0.049	0.098	0.049	0.098	0.195	0.781	0.098	0.098	0.098
E.c. DC 2	0.013	0.098	0.013	0.013	0.025	0.025	0.049	0.049	0.049	0.781	0.049	0.049	0.049
E.c. TEM	0.049	0.195	0.049	0.049	0.195	0.391	0.391	0.391	0.391	12.5	0.391	0.391	0.391
E.c. 1507 E	0.049	0.195	0.049	0.049	0.098	0.195	0.195	0.391	0.195	3.125	0.195	0.195	0.195
P.a. 1592 E	1.563	1.563	1.563	1.563	6.25	50	25	50	12.5	>100	25	25	12.5
P.a. 1771	1.563	1.563	1.563	1.563	3.125	25	6.25	25	12.5	>100	12.5	12.5	6.25
P.a. 1771M	0.391	0.391	0.391	0.391	0.781	1.563	0.781	25	12.5	100	12.5	12.5	6.25
S.t.	0.049	0.391	0.098	0.049	0.195	0.391	0.195	0.781	0.391	3.125	0.391	0.391	0.391
K.a. 1522 E	0.025	0.098	0.025	0.025	0.098	0.195	0.098	0.195	0.195	1.63	0.195	0.195	0.098
En.c. 1321 E	0.013	0.025	0.013	0.013	0.025	0.049	0.049	0.195	0.098	1.563	0.098	0.195	0.098

Abbreviation: CPR, cefpirome; CAZ, ceftazidime; *S.p., Streptococcus pyogenes; S.a., Staphylococcus aureus; E.c., Escherichia coli ; P.a., Pseudomonas aeruginosa; S.t., Salmonella typhimurium; K.a., Klebsiella aerogenes; En.c., Enterobacter cloacae.*

2a~**j** against selected Gram-positive and Gram-negative bacteria was determined by the agar dilution method. The results are summarized in Table 1 including those of cefpirome, ceftazidime and **1a** for comparison. Most cephalosporins prepared showed well-balanced activity against both Gram-positive and Gram-negative bacteria with diminished activity against *Pseudomonas* strains. They were more effective against Gram-positive bacteria than ceftazidime, but were similar to or less than cefpirome against all the strains tested. As a whole, substitution on the triazole ring failed to achieve favorable effects on the activity. The amino group was not crucial for activity in this series. Instead, substituents reduced the activity of these cephalosporins. Substantially the cephalosporins having a hydroxy substituent on the triazole ring (**2g**, **h**, **i**, **j**) showed inferior activity to the rest of the compounds. The most polar cephalosporin **2g** exhibited poor activity against both Gram-positive and Gram-negative bacteria. The compound **2a** carrying an unsubstituted triazole showed the best activity of the cephalosporins prepared in this study, comparable to cefpirome.

In conclusion, substitution of pyrazole in the 3-(pyrazol-3-yl)pyridiniummethylcephalosporins by triazole did not result in enhancement in the activity. Rather their activity seems to be dependent to the high polarity of the 3-(triazol-3-yl)pyridiniummethylcephalosporins. Further studies in this series will be focused on controlling their polarity.

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