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Journal of China Pharmaceutical University 1989; 20 (3): 129—135

SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 7β-(4, 7-DISUBSTITUTED COUMARIN-3-ACETAMIDO) CEPHALOSPORIN DERIVATIVES

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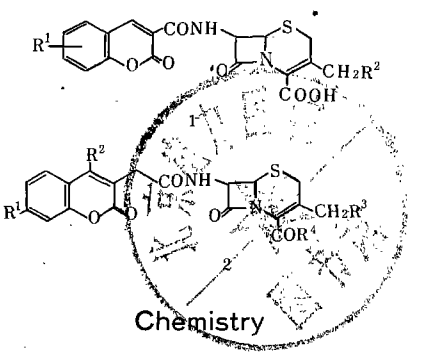
A series of 7β-(4, 7-disubstituted coumarin-3-acetamido) cephalosporin derivatives (2a-2m) were synthesized by acylation of 7-ACA, 7-ADCA, 7-ACT and a series of 3-(substituted phenylmethyl) cephalosporin nuclei (5c-5f) by 4, 7-disubstituted coumarin-3-acetic acid chloride. The nucleophilic displacement of 3-acetoxy group in 7-ACT with substituted phenols or in 2a with substituted pyridines to afford cephalosporin nuclei (5c-5f) or 3-(substituted pyriniomethyl)cephalosporin derivatives (2n and 2o), respectively, was also studied. Studies on the antimicrobial activity were extended to these 14 newly-synthesized cephalosporin derivatives. The minimum inhibitory concentration (MIC) values *in vitro* showed that all the compounds exhibit a significant activity against Gram-positive bacteria including penicillin-resistant strains.

Key words: antibiotics; cephalosporin; antibacterial activity; 4, 7-disubstituted coumarin-3-acetic acid; 3-(substituted phenylmethyl) cephalosporin nucleus.

The enormous clinical and commercial importance of cephalosporins has sustained a worldwide research effort directed at examining the effects of structural modifications on their biological properties. Changes in cephalosporin structure that have provided new clinical useful analogs are mostly confined to the variation of 7β-acylamino side chain and the 3-substituent. In the research of 7β-side chain which leads to novel cephalosporin derivatives, our colleagues have introduced some bioactive coumarin-3-formic acids to the 7β-position of cephalosporin nuclei, and reported a series of cephalosporin derivatives (1) which have some activities against Gram-positive bacterial [1, 2].

As part of our research program on novel cephalosporin antibiotics we therefore become interested in the synthesis of cephalosporin derivatives with a substituted coumarin-3-acetic acid as 7β-side chain and with a variety of 3-substituents.

We describe herein the synthesis of 4, 7-disubstituted coumarin-3-acetic acid intermediates and 3-[(substituted pheny) methyl]cephalosporin nuclei, their conversion into cephalosporin antibiotics and antimicrobial activity of the new cephalosporin derivatives with the general structure (2).

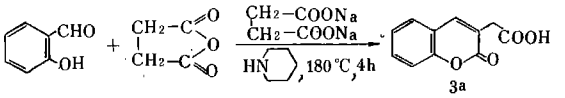


Coumarin-3-acetic acid(3a) was prepared by the method similar to Biman's [3], but some modifications in separation procedures were made (see scheme I). 7-Acyloxy-4-methylcoumarin-3-acetic acids (3b-3e) were synthesized from resorcinol by acid condensation, base hydrolization and acylation with acid chloride or acid anhydride as shown in scheme II.

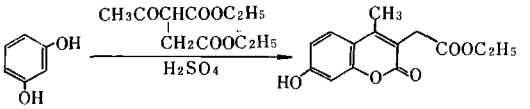
The nucleophilic displacement of the 3-acetoxy group in 5a by heterocyclic thiol in $BF_3 \cdot Et_2O$ [4] or by substituted phenols in TFA and $BF_3 \cdot Et_2O$ produced the cephalosporine nuclei 5b-5f bearing a thiomethyl group or a substituted phenylmethyl group at 3-position, respectively (see scheme III).

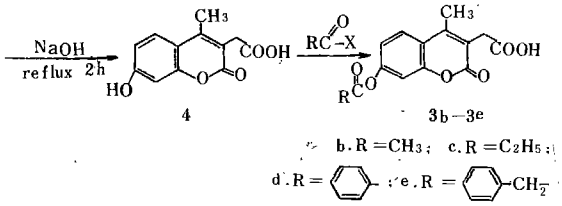
Received December 15, 1988

Scheme I

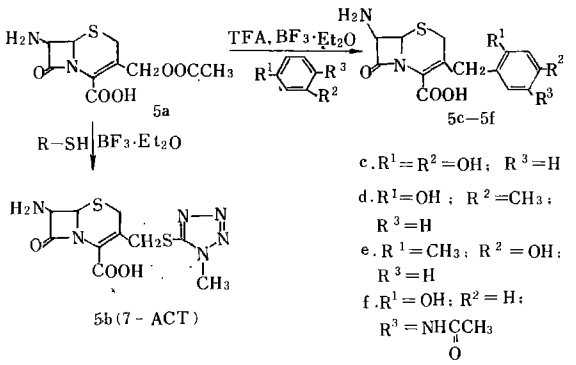


Scheme II

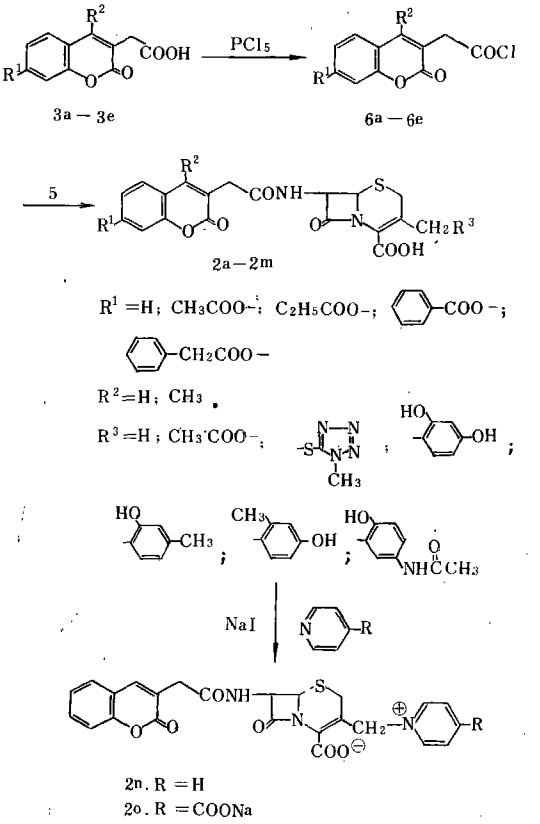




Scheme III



Scheme IV



The coupling of coumarin-3-acetic acids (3a-3e) to cephalosporin nuclei (5a-5f) was achieved via their acid chlorides formed with PCl_5 at ice bath temperature (see scheme Ⅳ).

Nucleophilic displacement of the 3-acetoxy group in 2a with substituted pyridines was performed in the usual way [5, 6] to afford the pyridinio compounds 2n and 2o.

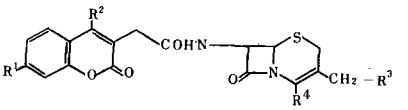
Cephalosporins (2a-2m) with a non-ionic substituent at 3-position were isolated and purified by centrifugal-thin-layer chromatography and Sephadex G-10 gel chromatography. However those (2n and 2o) with an ionic substituent at 3-position were isolated and purified by acetone precipitation, acid-base treatment and Sephadex G-10 and G-25 gel chromatography, since centrifugal-thin-layer chromatography, preparative reversed phase high-performance liquid chromatography and XAD-2 and XAD-4 adsorption chromatography failed to give pure targeted compounds.

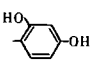
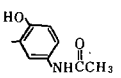
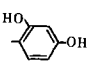
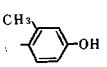
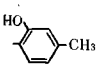
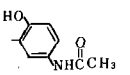
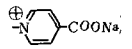
Antimicrobial Activity

The minimum inhibitory concentration (MIC) values of the 4, 7-disubstituted coumarin-3-acetamidocephalosporins (2b-2o) against selected strains of Gram-positive and Gram-negative bacteria were determined by the agar dilution technique [7]. Cefazolin and penicillin G were used as the reference compounds.

Table 1 lists the activity of the substituted coumarin-3-acetamidocephalosporins (2a-2o). All the compounds exhibit a significant activity against Gram-positive bacteria including penicillin-resistant strains. Those (2c and 2e) bearing a 1-methyl-1, 2, 3, 4-tetrazole-5-thiomethyl group at the

Tab 1. Minimum inhibitory concentration (MIC) values (μg/mL) of 7β-(4,7-disubstituted coumarin-3-acetamido) cephalosporins



					Test Organisms[a]							
2	R^1	R^2	R^3	R^4	I	II	III	IV	V	VI	VII	VIII
a[b]	H	H	$-OOCCH_3$	$-COOH$	0.08	0.39	0.31	NT[c]	NA[d]	NT	NA	NT
b	$C_6H_5CH_2COO-$	CH_3	H	$-COOH$	1.56	3.125	6.25	>200	>200	>200	>200	>200
c	$C_6H_5CH_2COO-$	CH_3		$-COOH$	0.0125	0.05	0.025	200	25	25	100	>200
d	$C_6H_5CH_2COO-$	CH_3	$-OOCCH_3$	$-COOH$	0.05	0.4	0.05	>200	>200	>200	>200	>200
e	C_2H_5COO-	CH_3		$-COOH$	<0.00625	0.2	0.05	100	50	100	100	>200
f	C_2H_5COO-	CH_3	$-OOCCH_3$	$-COOH$	0.1	0.1	<0.00625	200	100	200	200	>200
g	C_6H_5COO-	CH_3	$-OOCCH_3$	$-COOH$	0.8	6.25	0.4	>200	>200	>200	>200	>200
h	CH_3COO-	CH_3		$-COOH$	0.1	0.4	0.1	>200	>200	>200	>200	>200
i	CH_3COO-	CH_3		$-COOH$	0.1	0.4	0.2	>200	>200	>200	>200	>200
j	H	H		$-COOH$	0.2	0.78	0.78	>200	>200	>200	>200	>200
k	H	H		$-COOH$	0.0125	0.1	0.4	>200	>200	>200	>200	>200
l	H	H		$-COOH$	0.0125	0.2	0.2	>200	>200	>200	>200	>200
m	H	H		$-COOH$	0.4	1.56	0.4	>200	>200	>200	>200	>200
n	H	H		$-COO^{\ominus}$	0.1	0.4	0.4	100	50	50	100	>200
o	H	H		$-COO^{\ominus}$	0.1	1.56	1.56	>200	50	100	>200	>200
	Cefazolin				<0.00625	0.4	0.2	1.56	1.56	1.56	1.56	50
	Penicillin G				<0.00625	6.25	0.05	12.5	6.25	3.125	50	200

[a] I. *S. aureus* 209p, II. *S. aureus* Penicillin-resistant strain, III. *B. subtilis*, IV. *E. coli*, V. *S. typhi*, VI. *S. paratyphi* B, VII. *Shigella dysenteriae*, VIII. *P. vulgaris* OX-19. All the MIC valves against *P. aeruginosa* and *S. marcescens* are over 200 μg/ml. [b] from reference [8]. [c] No Activity. [d] Not Tested.

3-position showed a higher activity. In comparasion with others, those (2c, 2e, 2n and 2o) with a thiomethyl group or a substituted pyridiniomethyl group at the 3-position displayed a stronger activity against *E. coli*, *S. typhi*, *S. paratyphi* B and *Shigella dysenteriae*, but were much less active than cefazolin. All the newly-synthesized cephalosporins showed no favorable inhibitory effect on *P. aeruginosa*, *S. marcescens* and *P. vulgaris* OX-19. Further biological evalua-

tions on these cephalosporin derivatives remained to be made.

Experimental

Infrared spectra were obtained on a Nicolet 5 SXC FT-IR spectrometer. ^1H NMR spectra were obtained on a JEOL FX 90 (90MHz) NMR spectrometer. The data are listed in δ values (TMS: δ 0.00 or acetone δ 2.04).High-perfomance liquid chromatography (HPLC) was performed on a Shimadzu LC-6 HPLC instrument (solid phase: shim-pack ODs 6.0 mm $\varphi \times$ 1.5 m, moble phase: CH_3OH-H_2O, 4 :1). Melting points were uncorrected.

7-ACA (5a) and 7-ADCA (5g) were commercial products.

Minimum Inhibitory Concentration (MIC)

All the antibacterial activity *in vitro* is given as the MIC in μg/ml. The MIC's of cephalosporins were determined in two fold dilution by the agar dilution method. Nutrient agar (pH 7.4) was used as assay medium. The test organism was grown for 6 h on nutrient agar and one loopful of a suspension containing about 1 mg per ml of test organism was used as inoculum. MIC was determined after incubation at 37℃ for 24 h.

Coumarin-3-acetic Acid (3a)

Biman's method [3] was carried out with some modifications. After reacting at 180℃ for 4 h, the reactant was extracted with 95% ethanol, the extract evaporated, then extracted with 5% $NaHCO_3$ and the extract adjusted to pH 2 with 3 N HCl. The precipitate was collected by filtration and recrystallized from 95% ethanol. Yield 20—25%: mp 152—3℃.

7-Propionoxy-4-methylcoumarin-3-acetic Acid (3c)

To the freshly-distilled propionic anhydride (2 ml, 0.015 mol), 7-hydroxy-4-methylcoumarin-3-acetic acid (4) (0.5 g, 0.002 mol) was added. The mixture was heated to 90℃ and allowed to react for 1.5 h with stirring. After cooling, the reaction mixture was poured into ice-water. The resultant precipitate was collected by filtration and recrystallized from 30% ethanol to yield a white crystal: mp 165-6℃; Anal $C_{15}H_{14}O_6$, C 62.07 H 5.11 (Req C 62.07, H 4.83).

7-Acetoxy-4-methylcoumarin-3-acetic Acid(3b) was also obtained in the similar way as a white crystal: mp 199—200℃ [3].

7-Phenylacetoxy-4-methylcoumarin-3-acetic Acid (3e)

Compound 4 (0.5 g, 0.002 mol) was dissolved in anhydrous acetone (20 ml). To the resultant solution, one drop of pyridine and phenylacetyl chloride (0.41 g, 0.0026 mol) was added dropwise. The mixture was refluxed for 5 h. After the solvent was removed, the residue was dissloved in 5% $NaHCO_3$. The solution was washed with benzene and adjusted to pH 2 with 3 N HCl. A white precipitate was collected by filtration. Recrystallization from 95% ethanol gave the title compound 3e as a white crystal: mp 166—7℃; Anal $C_{20}H_{16}O_6$, C 67.97, H 4.33 (Req C 68.18, H 4.55).

7-Benzoxy-4-methylcoumarin 3-acetic Acid (3d) was also obtained by the similar method: mp 190—1℃ [9].

7-Amino-3-[(2-hydroxy-5-acetamidophenyl) methyl]cephalosporic Acid (5f)

To a solution of 5a (2.72 g, 0.01 mol) in TFA (20 ml), $BF_3 \cdot Et_2O$ (5.6 g, 0.04 mol) and *p*-acetamidophenol (1.64 g, 0.011 mol) were added. The mixture was allowed to react at 0—5℃ for 10 h. After the solvent was removed, the residue was dissolved in water (20 ml). The solution was adjusted to pH 3.5 with 28% ammonia aqueous solution in an ice-bath. After standing in ice-bath for an hour, the precipitate was filtered and washed thoroughly with water until the pH reached 6.5—7.0, and then with acetone to give a white powder. The sodium salt of the crude product was dissolved in water (2 ml) and the chromatography on a Sephadex G-10 column was carried out, using water as eluant. By the usual work-up procedure [10], the title compound 5f was obtained as a white powder: mp 199—201℃ (Dec.); IR (KBr) ν 3200, 1780, 1660, 1610, 1500, 1240 cm^{-1}; ^1H NMR (DMSO-D_6) δ 1.96 (s, 3H), 3.28 (dd, 2H), 3.68 (s, 2H), 4.63(d, 1H, J=5 Hz), 4.95 (d, 1H, J=5 Hz), 6.68 (d, 1H, J=8 Hz), 7.20 (dd, 1H, J=8 Hz; 3 Hz), 7.33 (d, 1H, J=3 Hz), 9.54 (s, 1H, exchangeable with D_2O).

The same method was used to prepare the

following compounds

7-Amino-3-[(2, 4-dihydroxyphenyl)methyl] cephalosporic Acid (5c)[11]

The title compound 5c was obtained as a white powder: mp 190—1℃; IR (KBr) ν 3350, 1770, 1605, 1500, 1400 cm^{-1}; ^1H NMR (DMSO—D_6) δ 3.25 (dd, 2H, J=18 Hz), 3.54 (s, 2H), 4.20 (d, 2H, J=5 Hz), 4.95 (d, 1H, J=5 Hz), 6.09 (d, 1H, J=3 Hz), 6.21 (dd, 1H, J=8 Hz; 3 Hz), 6.81 (dd, 1H, J=8 Hz).

The Mixture of 7-Amino-3-[(2-hydroxy-4-methylphenyl)methyl]cephalosporic Acid (5d) and 7-Amino-3-[(4-hydroxy-2-methylphenyl) methyl] cephalosporic Acid (5e) which was used without isolation.

The mixture was obtained as a white powder: mp 194—5℃; IR (KBr) ν 3350, 1770, 1650, 1500, 1400, 1340 cm^{-1}.

General Procedure for the Acylation of 7β-Aminoceph-3-em-4-carboxylic Acids (5) with an Acid Chloride (6)

Synthesis of cephalosporins 2a-2m: PCl_5 (0.005 mol) was dissolved in anhydrous methlene chloride (20 ml). To the solution, the side chain acid (3) (0.002 mol) was added. The mixture was allowed to react at 20℃ for an hour. After the solvent was removed, the solid was washed twice with petroleum ether to give the acid chloride (6).

To a solution of (5) (0.002 mol) and $NaHCO_3$ (0.002 mol) in water (20 ml) and acetone (20 ml) at -10℃, a solution of the acid chloride (6) discribed above in anhydrous acetone (20 ml) at -10℃ was added with stirring. At the same time an aqueous solution of 5% $NaHCO_3$ was added to maintain the pH at 7.5—7.8. Then the mixture was allowed to react with stirring at -10℃ for half an hour, at 0℃ for an hour and at 20℃ for 2 h. The reaction mixture was adjusted to pH 2 with 3 N HCl. The precipitate was filtered, washed thoroughly with water and dried *in vacuo* to give the crude (2). The crude product was subjected to chromatography on a Sephadex G—10 gel column using water as eluant. The appropriate fractions were lyophilized to give a white powder. The powder was then purified by chromatography on a centrifugal-thin-layer chromatography instrument, using GF254 silica gel as absorbant and methylene chloride-ethanol-glacial acetic acid (from 8 :1 :0.15 to 8 :4 :0.20) as eluant. The product-containing fractions were concentrated *in vacuo* to furnish the title compounds 2a-2m. The Anal. mp, IR and ^1H NMR data of compounds 2b-2m were listed in table 2. The data of compound 2a were published otherwhere [8].

General Procedure for Displacement at the 3-Position with Substituted Pyridines

Synthesis of cephalosporins 2n and 2o: To a suspension of 2a (0.001 mol) and substituted pyridine (0.002 mol) in water (3 ml), $NaHCO_3$ was added to prepare a solution and to adjust the pH to 6.5. After sodium iodide (1.65 g, 0.011 mol) was added, the mixture was stirred at 70℃ for 2 h. When cooled, the reaction solution was poured with stirring into acetone (200 ml) under ice-cooling. The mixture was allowed to stand overnight in a refrigerator. A solid was formed and collected. The solid was reprecipitated by dissolving in water and then poured into acetone. The reprecipitation was repeated until no iodic ion could be detected. Then the precipitate was dissolved in water and chromatographed on a Sephadex G-10 gel colum with water as eluant. The fractions containing the desired product (detected by HPLC and TLC) were collected and adjusted to pH 2 with 3 N HCl. After stirring for 30 min, a precipitate was removed by filtration. The filtrat was then adjusted to pH 7 with dilute NaOH solution and lyophilized to give a white powder. The powder was rechromatographed on Sephadex G-10 and G-25 gel columns using water as eluant. The product-containing fractions were collected and lyophilized. The rechromatography on Sephadex G-10 and G-25 gel columns was repeated until no impurity could be detected by HPLC and IR spectra. Then the title compound was obtained as a white powder. Their Anal. mp, IR and ^1H NMR data were listed in table 2.

Acknowledgments

The authors express their gratitude to Physicochemical Analysis Laboratory in China Pharmaceutical University, to Modern Analysis Center in Nanjing University and to Jiansu Institute of

Tab 2. Mp. Anal. IR and ^{1}HNMR data of compounds 2b-2o

2	mp ℃	Formula	Anal Caled	Anal Found	IR ν cm^{-1}	^{1}HNMR (D_6-DMSO) δ ppm
b	152-3	$C_{28}H_{24}N_2O_8S \cdot 0.5H_2O$	C 60.31 H 4.48 N 4.82	60.39 4.47 4.82	3400,3150, 1750, 1700, 1640, 1600, 1210, 1100.	8.91(1H,d), 7.85(1H,d), 7.32(5H,s), 7.22(1H,dd), 7.10(1H,d), 5.55(1H,dd), 5.02(1H,d), 4.00(2H,s), 3.63(1H,s), 3.43(2H,dd), 2.35(3H,s), 2.01(3H,s).
c	166-8	$C_{30}H_{26}N_6O_8S_2$	C 52.93 H 4.12 N 12.35	52.84 4.21 12.60	3400, 1760, 1700, 1650, 1600, 1530, 1210.	8.95(1H,d), 7.84(1H,d), 7.44(5H,s), 7.21(1H,dd), 7.09(1H,d), 5.61(1H,dd), 5.02(1H,d), 4.28(2H,s), 3.99(2H,s), 3.90(3H,s), 3.65(2H,dd), 3.62(2H,s), 2.35(3H,s).
d	155-6	$C_{30}H_{26}N_2O_{10}S \cdot H_2O$	C 57.42 H 4.29 N 4.62	57.39 4.11 4.28	3400, 3260, 1760, 1700, 1650, 1600, 1530, 1210.	8.95(1H,d), 7.85(1H,d), 7.32(5H,s), 7.20(1H,dd), 7.10(1H,d), 5.62(1H,dd), 5.05(1H,d), 4.82(2H,dd), 3.98(2H,s), 3.62(2H,s), 3.50(2H,dd), 2.35(3H,s), 2.00(3H,s).
e	185-6	$C_{25}H_{24}N_6O_8S_2$	C 49.99 H 4.00 N 14.00	49.93 3.83 13.35	3350, 1780, 1740, 1708, 1660, 1605, 1540, 1230.	8.95(1H,d), 7.85(1H,d), 7.20(1H,d), 7.15(1H,dd), 5.62(1H,dd), 5.03(1H,d), 4.28(2H,s), 3.91(3H,s), 3.62(2H,s), 3.63(2H,dd), 2.62(2H,q), 2.38(3H,s), 1.13(3H,t).
f	181-2	$C_{25}H_{24}N_2O_{10}S$	C 55.14 H 4.41 N 5.15	54.68 4.52 5.28	3400, 3250, 1780, 1750, 1708, 1650, 1600, 1235.	8.95(1H,d), 7.83(1H,d), 7.23(1H,d), 7.20(1H,dd), 5.65(1H,dd), 5.07(1H,d), 4.85(2H,dd), 3.63(2H,s), 3.52(2H,dd), 2.62(2H,q), 2.01(3H,s), 1.15(3H,t).
g	196-7	$C_{29}H_{24}N_2O_{10}S$	C 58.53 H 3.83 N 4.88	58.06 3.85 4.45	3400, 1750, 1710, 1600, 1250, 1210,	8.98(1H,d), 7.20-8.20(8H,m), 5.65(1H,dd), 4.85(2H,dd), 3.65(2H,s), 3.55(2H,dd), 2.40(3H,s), 5.08(1H,d), 2.00(3H,s).
h	229-30	$C_{28}H_{24}N_2O_{10}S \cdot 3H_2O$	C 52.99 H 4.73 N 4.41	53.07 4.83 4.47	3400, 1760, 1700, 1620, 1510, 1205.	8.85(1H,d), 7.90(1H,d), 7.18(1H,d), 7.10(1H,dd), 6.78(1H,d), 6.02(1H,dd), 6.00(1H,d), 5.42(1H,dd), 4.93(1H,d), 3.55(2H,s), 3.35(2H,s), 3.00(2H,dd), 2.30(3H,s), 2.27(3H,s).
i	210-1	$C_{30}H_{27}N_3O_{10}S \cdot 2H_2O$	C 54.79 H 4.72 N 6.39	54.70 4.70 6.08	3400, 1760, 1710, 1705, 1700, 1650, 1605, 1200.	9.58(1H,s), 8.90(1H,d), 7.28(1H,d), 7.05-7.30(4H,m), 6.52(1H,d), 5.48(1H,dd), 4.97(1H,d), 3.57(2H,s), 3.25(2H,s), 3.10(2H,dd), 2.32(3H,s), 2.28(3H,s), 1.98(3H,s).
j	138-9	$C_{25}H_{20}N_2O_8S \cdot 2.5H_2O$	C 54.24 H 4.52 N 5.06	54.46 4.48 4.32	3370, 1750, 1700, 1600, 1500, 1400, 1350, 1170.	8.90(1H,d), 7.88(1H,s), 7.20-7.70(4H,m), 6.80(1H,d), 6.06(1H,dd), 6.02(1H,d), 5.46(1H,dd), 4.95(1H,d), 4.15(2H,dd), 3.42(2H,s), 3.00(2H,dd).
k	91-2	$C_{26}H_{22}N_2O_7S \cdot 1.5H_2O$	C 58.53 H 4.72 N 5.25	58.62 4.25 4.90	3300, 1775, 1710, 1650, 1600, 1500, 1220, 1180.	8.98(1H,d), 7.92(1H,s), 7.20-7.70(4H,m), 6.92(1H,d), 6.52(1H,d), 6.50(1H,dd), 5.58(1H,dd), 5.02(1H,d), 3.65(2H,s), 3.47(2H,s), 3.17(2H,dd), 2.11(3H,s).
l	94-5	$C_{26}H_{22}N_2O_7S \cdot 2.5H_2O$	C 56.62 H 4.90 N 5.08	56.62 5.42 4.77	3300, 1760, 1710, 1600, 1560, 1500, 1400, 1180.	8.92(1H,d), 7.88(1H,s), 7.20-7.70(4H,m), 6.90(1H,d), 6.50(1H,dd), 6.45(1H,d), 5.50(1H,dd), 4.97(1H,d), 3.42(2H,s), 3.30(2H,s), 3.17(2H,dd), 2.08(2H,s).
m	204-5	$C_{29}H_{23}N_3O_8S \cdot 2H_2O$	C 55.38 H 4.27 N 6.78	55.34 4.54 6.78	3400, 3250, 1760, 1705, 1650, 1600, 1540, 1500.	9.52(1H,s), 8.90(1H,s), 7.86(1H,s), 7.40-7.70(4H,m), 7.30(1H,d), 7.20(1H,dd), 6.53(1H,d), 5.50(1H,dd), 4.98(1H,d), 4.08(2H,dd), 3.35(2H,dd), 2.95(2H,s), 1.93(3H,s).
n	>300	$C_{24}H_{19}N_3O_6S \cdot 2H_2O$	C 56.13 H 4.51 N 8.18	55.97 4.19 7.79	3400, 1765, 1710, 1605, 1490, 1220.	8.20-8.80(5H,m), 7.90(1H,s), 7.20-7.70(4H,m), 5.50(1H,d), 4.95(1H,d), 5.25(2H,dd), 3.60(2H,s), 3.20(2H,dd). (in D_2O)
o	>300	$C_{25}H_{18}N_2O_8SNa \cdot 2H_2O$	C 51.81 H 3.80 N 7.25	51.67 3.73 6.48	3400, 1760, 1710, 1610, 1540, 1240.	8.90(2H,d), 8.10(2H,d), 7.76(1H,s), 7.10-7.60(4H,m), 5.55(1H,d), 5.30(2H,dd), 5.02(1H,d), 3.45(2H,s), 3.25(2H,dd). (in D_2O)

Chemical Engineering for IR and ^{1}H NMR spectroscopic measurement and for the elemental analysis. Thanks are also due to Prof. Cheng Pongbao for instructing antimicrobial tests.

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7β-(4，7-二取代香豆素-3-乙酰胺基)头孢菌素衍生物的合成及抗菌活性

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摘 要 以4，7-二取代香豆素-3-乙酸为侧链酸，用酰氯法与7-ACA，7-ADCA，7-ACT及一系列的3-取代苯甲基头孢母核（5c－5f）进行缩合，合成了一系列7β-（4，7-二取代香豆素-3-乙酰胺基）头孢菌素衍生物（2a－2m）。并且研究了7-ACA的3位乙酰氧基被取代酚取代及2a的3位乙酰氧基被取代吡啶取代的亲核取代反应，分别合成了一系列3-取代苯甲基头孢母核（5c－5f）及3-取代吡啶离子甲基头孢菌素衍生物（2n，2o）。体外抑菌活性试验结果表明，所合成的14个新的头孢菌素衍生物对包括青霉素耐药菌株在内的革兰氏阳性菌都有较强的抑菌作用。

关键词 抗生素；头孢菌素；抗菌活性；4，7-二取代香豆素-3-乙酸；3-取代苯甲基头孢母核

本 刊 声 明

本刊1988年第4期发表的《应用生化转化法由血红素制备胆红素》一文，介绍了本校生化教研室吴梧桐副教授等研制的由猪血制取胆红素的方法。最近发现有人复制本文资料，非法高价出售；湖南某生化厂还盗用本校生化教研室名义举办“猪血制备胆红素”培训班。就此，本刊特郑重声明如下：一、吴梧桐副教授等研制的由猪血制备胆红素的方法，已在实验室获得成功。尽管发表的该文较为详细，但光凭这些资料无法生产出合格的胆红素产品，更不能所谓“大批量生产”。敬请各界切勿上当！二、盗用本校生化教研室名义办培训班或复制材料高价出售，均为非法行为，由此产生的一切后果由有关当事人负责。三、本校生化教研室已设计并试验成功由猪血制备胆红素的简易方法，并在进一步完善中。如需进行技术转让和有关技术咨询，请与本刊联系。

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