SYNTHESIS AND BIOLOGICAL EVALUATION OF A 4-FLUOROMETHYL MONOBACTAM ANALOG

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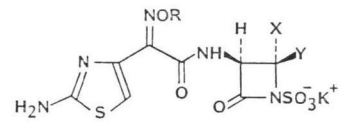
(Received for publication May 24, 1983)

The synthesis and *in vitro* antibacterial activity of (±)(*cis*)-3-[2-(2-aminothiazol-4-yl)-(*Z*)-2-methoxyiminoacetamido]-4-fluoromethyl-2-oxo-1-azetidinesulfonic acid, potassium salt are presented.

The introduction of a methyl substituent at C-4 in the monobactam molecule has provided compounds (*e.g.* **1** and **2**) which display potent activity against a broad spectrum of Gram-negative organisms as well as good β-lactamase stability. One member of this family of antibiotics, aztreonam (**1b**), is being developed for clinical use.[1] In an effort to further define the structure-activity parameters of this class of compounds, we have initiated a program directed at the synthesis and biological evaluation of 4-fluoromethyl monobactam analogs **3** and **4**. Herein, we describe a brief synthesis of **4a** and report on its antimicrobial activity.

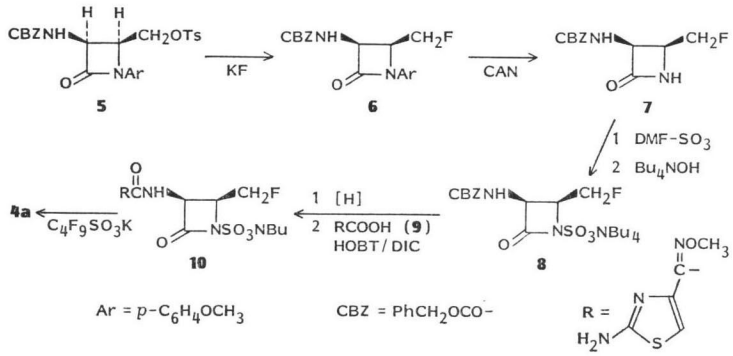


1: X=CH_3, Y=H
2: X=H, Y=CH_3
3: X=CH_2F, Y=H
4: X=H, Y=CH_2F

Series **a**: R=CH_3
b: R=$C(CH_3)_2COOH$

The strategy for the preparation of the title compound involves initial construction of an appropriately functionalized β-lactam nucleus, introduction of fluorine, and elaboration to the final target molecule. The synthesis of a suitable β-lactam precursor, tosylate **5**, has been reported recently by KRONENTHAL and coworkers.[2]

Treatment of **5** with excess potassium fluoride in refluxing acetonitrile (15 hours) containing 18-crown-6[3] afforded fluoride **6**, albeit in low yield (23%) which was purified by high performance liquid chromatography. Oxidative dearylation of **6** was accomplished in 83% yield employing ceric ammonium



nitrate (CAN)[2,4] to provide **7**. Reaction of **7** with dimethylformamide-sulfur trioxide complex (DMF-SO_3),[5] followed by treatment with tetra-*n*-butylammonium hydroxide furnished **8** (76%). Hydrogenolysis of the CBZ-protecting group, followed by coupling with 2-(2-aminothiazol-4-yl)-(*Z*)-2-methoxyiminoacetic acid (**9**)[6] in dimethylformamide containing 1-hydroxybenzotriazole (HOBT) and *N*,*N*-diisopropylcarbodiimide (DIC) by a modification of the literature procedure[7] afforded **10** which was not isolated. Removal of the solvent under high vacuum followed by treatment of an acetone solution of crude **10** with potassium nonafluorobutane sulfonate,[7] resulted in immediate precipitation of (±) (*cis*)-3-[2-(2-aminothiazol-4-yl)-(*Z*)-2-methoxyiminoacetamido]-4-fluoromethyl-2-oxo-1-azetidinesulfonic acid, potassium salt (**4a**, 60%), which was submitted for biological testing without further purification.[5]

Table 1. *In vitro* antibacterial activity of compound **4a***.

Organism	Strain	MIC (μg/ml)
Staphylococcus aureus	29213	>256
Streptococcus faecalis	29212	>256
Enterobacter cloacae	13047	0.25
Escherichia coli	25922	0.06
Klebsiella pneumoniae	KL-1	0.125
Proteus vulgaris	589	0.06
Pseudomonas aeruginosa	27853	64
Serratia marcescens	13880	0.25

* Compound **4a** was evaluated as a mixture of racemates. The MIC values reported were obtained by the microdilution broth method and are normalized.

Although less potent than aztreonam (**1b**), **4a** has demonstrated excellent activity *in vitro* against a variety of Gram-negative bacteria. By contrast, **4a** was relatively ineffective against Gram-positive organisms. These data are illustrated in Table 1.

Experimental

The melting points were obtained on a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses were performed with a Perkin-Elmer Model 240 elemental analyzer by the Analytical Section of these laboratories. IR spectra were recorded on a Perkin-Elmer 299 infrared spectrophotometer. NMR spectra were obtained on a Varian FT-80A NMR spectrometer with Me_4Si as the internal standard. Mass spectra were recorded with an Associated Electrical Industries MS-9 high resolution mass spectrometer.

(±)(*cis*)-3-[2-(2-Aminothiazol-4-yl)-(*Z*)-2-methoxyiminoacetamido]-4-fluoromethyl-2-oxo-1-azetidinesulfonic Acid, Potassium Salt (**4a**)

A mixture of 300 mg (0.52 mmol) of carbamate **8**, 300 mg of 10% palladium on carbon, and 14 ml of anhydrous dimethylformamide was treated under one atmosphere of hydrogen at ambient temperature for 2.5 hours. The reaction mixture was filtered and to the resulting solution was added 85 mg (0.63 mmol) of 1-hydroxybenzotriazole, 85 mg (0.67 mmol) of *N*,*N*-diisopropylcarbodiimide, and 120 mg (0.6 mmol) of 2-(2-aminothiazol-4-yl)-(*Z*)-2-methoxyiminoacetic acid (**9**)[6] and the reaction mixture was stirred overnight at ambient temperature. The solvent was removed by distillation and the residue was dissolved in 14 ml of acetone. To the solution was added in one portion a solution of 300 mg (0.89 mmol) of potassium monofluorobutane sulfonate and 5 ml of acetone. The resulting precipitate was collected by repeated centrifugation and decanting to give 91 mg (42%) of **4a** as an off-white solid. The original mother liquor was triturated with ethyl ether to afford an additional 40 mg (18%) of product: IR (KBr) 3440, 3340, 3220, 1775, 1675, 1620, 1540, 1280, 1260, 1060, and 660 cm^{-1}; ^1H NMR (DMSO-d_6+D_2O) 6.7 (s, 1H, hetero *H*), 5.30~3.90 (complex m, 4H, $-CH_2F$, C-3H, and C-4H), and 3.8 (s, 3H, $-C=NOCH_3$).

(±)(*cis*)-3-(Benzyloxycarbonylamino)-4-fluoromethyl-1-(4-methoxyphenyl)-2-oxo-1-azetidine (**6**)

A mixture of 1.2 g (2.35 mmol) of tosylate **5**, 600 mg (10.3 mmol) of freshly dried potassium fluoride, 400 mg of 18-crown-6, and 15 ml of anhydrous acetonitrile was heated at reflux for 15 hours. The reac-

tion mixture was allowed to cool to ambient temperature, diluted with water, and extracted with methylene chloride. The combined organic extracts were washed with saturated sodium chloride solution and dried over sodium sulfate. The solvent was removed under reduced pressure to afford a pasty yellow solid, which was applied to a silica gel column. Elution with ethyl acetate - hexanes (1: 3) furnished a light tan solid which was purified further by high performance liquid chromatography (silica gel; ethyl acetate - hexanes, 1: 4) to give 190 mg (23%) of **6** as a white solid: mp 173~175°C; IR (KBr) 3310, 1750, 1700, 1550, 1520, 1330, 1260, 1070, and 830 cm^{-1}; ^1H NMR ($CDCl_3$) 7.5~6.75 (m, 10H, ArH and -NH), 5.8~4.15 (m, 4H, $-CH_2F$, C-3H, and C-4H), 5.15 (s, 2H, $PhCH_2O-$), and 3.80 (s, 3H, $-OCH_3$); mass spectrum *m/z* 358.

Anal. Calcd. for $C_{19}H_{19}N_2O_4F$: C 63.67, H 5.34, N 7.81, F 5.30.
Found: C 63.38, H 5.38, N 7.68, F 5.22.

(±)(*cis*)-3-(Benzyloxycarbonylamino)-4-fluoromethyl-2-oxo-1-azetidine (**7**)

To a mixture of 380 mg (1.1 mmol) of fluoride **6** and 30 ml of acetonitrile, cooled to −5°C, was added portionwise a solution of 1.8 g (3.3 mmol) of ceric ammonium nitrate and 18 ml of water. The reaction mixture became homogeneous and was stirred at this temperature for 0.5 hour, diluted with water and extracted with ethyl acetate. The combined organic extracts were washed sequentially with saturated sodium bicarbonate solution, 10% sodium sulfite solution, and saturated sodium bicarbonate solution, dried over sodium sulfate and concentrated under reduced pressure to furnish 230 mg (83%) of **7** as a light tan solid: mp 163~164°C; IR (KBr) 3330, 1750, 1685, 1550, 1260, and 1070 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.5~8.3 (brs, 1H, -NH), 8.10~7.85 (m, 1H, -NH), 5.05 (s, 2H, $PhCH_2O-$), and 5.0~3.4 (complex m, 4H, $-CH_2F$, C-3H, and C-4H), mass spectrum *m/z* 253 (M+H).

Anal. Calcd. for $C_{12}H_{13}N_2O_3F$: C 57.14, H 5.19, N 11.11.
Found: C 57.23, H 5.26, N 10.58.

(±)(*cis*)-3-(Benzyloxycarbonylamino)-4-fluoromethyl-2-oxo-1-azetidinesulfonic Acid, Tetrabutylammonium Salt (**8**)

To a solution of 245 mg (0.97 mmol) of carbamate **7** and 2.7 ml of anhydrous dimethylformamide at ambient temperature was added 1.9 ml of dimethylformamide-sulfur trioxide complex[7] (1.5 M). The solution was stirred for 6 hours, cooled to 0~5°C, and diluted with water and methylene chloride. To the mixture was added dropwise tetra-*n*-butylammonium hydroxide until pH 13. The reaction mixture was extracted with methylene chloride. The combined organic extracts were washed with water (4×), dried over sodium sulfate, and concentrated *in vacuo* to give 420 mg (76%) of **8** as an amber oil. This oil was further purified by application to a silica gel column. Elution with methanol - methylene chloride (1: 9) and combination of appropriate fractions provided 310 mg (56%) of **8** as an amber oil: IR (neat) 3300, 1780, 1720, 1510, 1490, 1460, 1270 (br), 1160, and 650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35 (s, 5H, ArH), 5.85~4.0 (m, 5H, $-CH_2F$, C-3H, C-4H, -NH), 5.12 (s, 2H, $PhCH_2O-$), 3.45~3.0 (m, 8H, $-N(CH_2CH_2CH_2CH_3)_4$), 1.85~1.15 (m, 16H, $-N(CH_2CH_2CH_2CH_3)_4$), and 1.1~0.8 (dist-t, 12H, $-N(CH_2CH_2CH_2CH_3)_4$).

Anal. Calcd. for $C_{28}H_{48}N_2O_6FS$: C 58.61, H 8.43, N 7.32.
Found: C 58.93, H 8.28, N 6.84.

Acknowledgments

The authors are grateful to the Analytical Section of these laboratories for providing spectral and microanalytical data, Ms. BARBARA ZINCK and Ms. ALICE GERMAN for high performance liquid chromatographic purification of intermediate **6**, Mr. GEORGE CONKLIN and Mr. DANIEL DELECKI for the preparation of intermediate **9** and dimethylformamide-sulfur trioxide complex respectively. We thank Dr. DONALD P. STRIKE for helpful discussions.

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