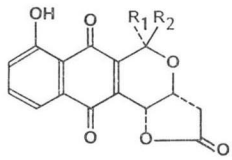
ANTICOCCIDIAL ACTIVITY OF FRENOLICIN B AND ITS DERIVATIVES

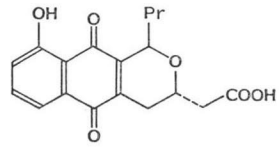
Sir:

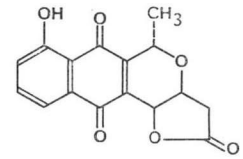
In the course of searching for effective antibiotics on chicken coccidiosis which causes a serious problem in the poultry industry, frenolicin B[1] (**1**), a naphthoquinone antibiotic produced by *Streptomyces roseofulvus* was found to exhibit an excellent anticoccidial activity. On the other hand, deoxyfrenolicin[2] (**2**), which is co-produced by the organism and chemically transformed to frenolicin B *via* a quinone methide intermediate[3] by air oxidation, is virtually devoid of the activity. The present communication describes anticoccidial activities of **1** and its related compounds.

Naturally occurring quinone antibiotics containing a fused pyrano-γ-lactone ring system such as **1** can be classified into two groups, kalafungin[4] (**3**) type and nanaomycin D[5] (**4**) type, on the basis of the stereochemistry at C-1, 3 and 4 of the pyran ring. These are an enantiomeric pair and **1** belongs to kalafungin type. On treatment with pyridine at room temp for 20 hours, the propyl group at C-1 of **1** epimerized quantitatively to yield 1-epifrenolicin B (**5**): mp 174~175°C; $[\alpha]_D^{20}$ +200° (*c* 1.0, $CHCl_3$); ^1H NMR (90 MHz, $CDCl_3$) 1.00 (3H, t, J=7 Hz), 1.68 (4H, m), 2.82 (2H, ABX, J_{AB}=16.9 Hz, J_{AX}=4.9 Hz, J_{BX}=0 Hz), 4.62 (1H, dd, J=4.9 and 2.7 Hz), 4.90 (1H, dd, J=9.3 and 4.4 Hz), 5.24 (1H, d, J=2.7 Hz), 7.29 (1H, m), 7.68 (2H, m).

To test the anticoccidial efficacy, eight day-old chicks were used. Samples were administered







Frenolicin B (**1**) R_1 = H, R_2 = $(CH_2)_2CH_3$

Kalafungin (**3**) R_1 = H, R_2 = CH_3

1-Epifrenolicin B (**5**) R_1 = $(CH_2)_2CH_3$, R_2 = H

Deoxyfrenolicin (**2**)

Nanaomycin D (**4**)

Table 1. The effect of frenolicin B and its related compounds on *Eimeria tenella* infection in chicks.

Drug concentration in feed	Survival (%)	Relative weight gain (%)	Relative oocyst production	Mean lesion score of cecum	ACI[a]
Frenolicin B (**1**) 60 μg/g	100	96.4	0	0	196.4
1-Epifrenolicin B (**5**) 60 μg/g	100	86.3	10	15	161.3
Deoxyfrenolicin (**2**) 100 μg/g	100	49.8	40	40	69.8
Kalafungin (**3**) 60 μg/g	100	80.8	10	20	150.8
Nanaomycin D (**4**) 60 μg/g	100	84.0	40	23.3	120.7
Salinomycin 50 μg/g	100	99.3	0	0	199.3
Infected unmedicated control	100	58.9	40	40	78.9
Uninfected unmedicated control	100	100	0	0	200

[a] ACI=(survival+relative weight gain)−(relative oocyst production+mean lesion score of cecum).
Score: 180~200, effective; 160~180, moderately effective; 120~160, slightly effective; 0~120, not effective.

by addition to the diet with appropriate concentrations. At the two days after the feeding was started, chicks were infected by oral intubation with 5,000 sporulated oocyst of *Eimeria tenella*. The observation periods were seven days after the infection and at its termination survival rate and average weight gain of infected-medicated chicks were calculated comparing with those of uninfected-unmedicated control. Coccidial lesions of the cecum were scored by the method of JOHNSON *et al.*[6]. The number of oocyst per gram of feces was counted at the five and seven days after the infection comparing with those of infected-unmedicated control. To determine the total efficacy of a drug on coccidiosis ACI[7] (anticoccidial index) was adopted as a criteria. The anticoccidial activities of **1** and its related compounds are summarized in Table 1.

Frenolicin B (**1**) showed excellent protective effect against *E. tenella* comparable to salinomycin, which is a polyether antibiotic useful in the treatment of coccidial infections of poultry. The lack of the lactone portion presented by the structure of **2** resulted in substantial inactivation. The epimerization at C-1 on the pyran ring of **1** to afford the more stable conformer **5** brought about the reduction of the activity. It is noteworthy that kalafungin (**3**) containing the same configuration at C-1, 3 and 4 on the pyran ring as **1** exhibited relatively good anticoccidial efficacy, while its enantiomer **4** is virtually inactive. These results indicate that the existence of the lactone ring and the stereochemistry at C-1, 3 and 4 on the pyran ring of **1** are important factors for manifestation of anticoccidial activity.

Acknowledgments

The authors wish to thank Dr. J. E. GRADY of the Upjohn Co. for the generous gift of kalafungin.

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(Received July 8, 1985)

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