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Synthesis and biological activity of 2-hydroxynicotinoyl-serine-butyl esters related to antibiotic UK-3A

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ABSTRACT

Novel 2-hydroxynicotinoyl-serine-butyl esters have been synthesized. Three-step reactions from L-serine by esterification with *n*-butanol, amidation with 2-hydroxynicotinic acid and esterification with the corresponding carboxylic acids gave **AD-1**, **AD-2** and **AD-3**. The toxicity level of esters were determined by Brine shrimp assay, and antibiotic activity was tested against *Escherichia coli*, *Bacillus subtilis*, *Staphylococcus aureus* and *Candida albicans*. **AD-3** showed greater activity as a growth inhibitor of *B. subtilis* and *S. aureus* compared to Antimycin A_3.

Recently, research on antifungal antibiotic agents has become more important in medicinal chemistry, because many infectious diseases caused by fungi or bacteria have shown resistance to current antibiotics. To meet this challenge, research and development of new antifungal antibiotic agents is needed.[1] However, random development and synthesis of new antibiotic agents can be expensive and time-consuming. Consequently, synthesis of antibiotic analogues has emerged as a promising strategy to seek new antibiotic agents that are effective against pathogenic microorganisms. Analogue synthesis is advantageous due to its short duration and high probability of yielding a more active compound by modifying the structure, and it also gives information about the structure–activity relationship. In 1997, Ueki and co-workers succeeded in isolating the novel UK-3A compound which demonstrated antibiotic and antifungal activity from *Streptomyces* sp. 517-02.[2–4] The structure of UK-3A that consist of a nine-membered dilactone is similar to well-known Antimycin A_3, an antibiotic and insecticide which has also been isolated from *Streptomyces* sp. in 1949[5,6] (Fig. 1).

The significant antibiotic antifungal activity of UK-3A, prompted us to carry out the synthesis of 2-hydroxynicotinoyl-serine-butyl esters related to UK-3A which have simple structure, but are expected to have higher bioactivities than the original compound UK-3A. In this research, we modified the structure of UK-3A by opening the nine-membered dilactone ring system, varying the side chain of the ester group and replacing 3-hydroxypicolinate moiety to commercially available and inexpensive 2-hydroxynicotinate moiety.

We proposed a three-step synthesis reaction of 2-hydroxynicotinoyl-serine butyl esters, compound **AD-1**, **AD-2** and **AD-3** (Scheme 1). The first step is the esterification of L-serine (**1**) with *n*-butanol by using *p*-toluensulfonic acid as a catalyst, yielding 51% of serine-butyl ester *p*-TsOH (**2**). In the second step, the combination of DCC and DMAP[7–9] is used to the formation of 2-hydroxynicotinoyl-serine-butyl ester (**4**) from the coupling reaction between **2** and 2-hydroxynicotinic acid (**3**). Subsequently, the third step proceeded with three different reactions, in which 2-hydroxynicotinoyl-serine-butyl ester (**4**) is reacted with acetic anhydride, 3-phenylpropionic acid and octanoic acid to produce **AD-1**, **AD-2** and **AD-3** in 69%, 43% and 69% yields, respectively.

Antibiotic activity of 2-hydroxynicotinoyl-serine-butyl esters and Antimycin A_3 are summarized in Table 1. Antibiotic activity of each ester and Antimycin A_3 (standard) were tested against *Escherichia coli*, *Bacillus subtilis*, *Staphylococcus aureus* and *Candida albicans*. The result showed that **AD-1**, which contains an acetyl group, has lower antibiotic activity than Antimycin A_3 on *E. coli* and *C. albicans*, and is equally active with Antimycin A_3 on *B. subtilis* and *S. aureus*. **AD-2** which bears a phenyl group, has lower antibiotic activity than Antimycin A_3 on all the microorganism tested. Whereas, **AD-3**, which contains an octanoyl group with MIC values of 50 ppm and 100 ppm on *B. subtilis* and *S. aureus*, respectively, has higher antibiotic activity than Antimycin A_3

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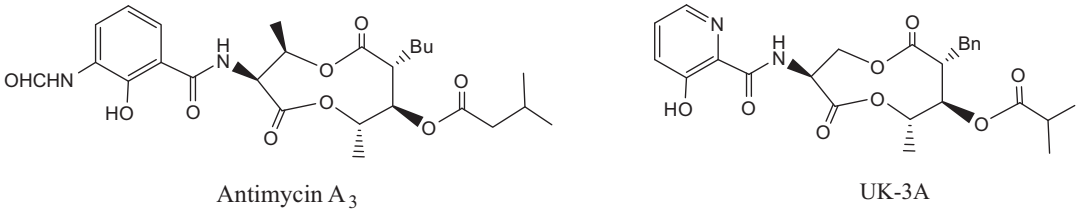
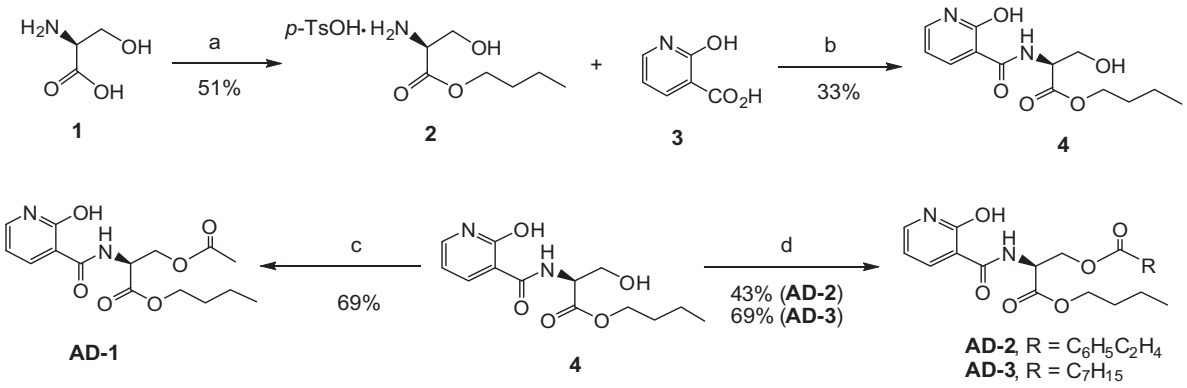


Figure 1. Structure of Antimycin A_3 and UK-3A.



Scheme 1. Synthesis of 2-hydroxynicotinoyl-serine-butyl esters. Reagent and conditions: (a) *n*-butanol, *p*-TsOH, benzene, 110 °C, 24 h; (b) DCC, DMAP, pyridine, 55 °C, 24 h; (c) acetic anhydride, pyridine, rt, 4 h; (d) RCO_2H (**AD-2**, R = $C_6H_5C_2H_4$; **AD-3**, R = C_7H_{15}), DCC, DMAP, rt, 4 h.

Table 1
Antibiotic activity of **AD-1**, **AD-2**, **AD-3** and Antimycin A_3

Compounds	Antibiotic activity, MIC (diameter of inhibition)[a]			
	E. coli	*B. subtilis*	*S. aureus*	*C. albicans*
AD-1	250 (7.00)	250 (7.00)	250 (7.50)	500 (7.50)
AD-2	1000 (7.83)	500 (7.00)	1000 (7.50)	1000 (7.50)
AD-3	75 (7.00)	50 (7.00)	100 (7.00)	250 (7.83)
Antimycin A_3	50 (7.00)	250 (8.50)	250 (8.00)	50 (10.00)

[a] MIC, minimum inhibitory concentration in ppm, diameter of inhibition (mm) is given in parentheses.

Table 2
Brine shrimp assay of **AD-1**, **AD-2** and **AD-3** against *Artemia salina*

Compounds	% of mortality in various concentration[a] (ppm)				Toxicity LC_{50} (ppm)
	100	250	500	1000	
AD-1	4.94 (±4.29)	9.70 (±10.01)	39.62 (±14.42)	58.66 (±16.21)	811.01
AD-2	26.67 (±5.77)	55.58 (±2.41)	76.67 (±5.77)	100	266.83
AD-3	0	0	2.78 (±4.81)	11.02 (±3.95)	3620.41

[a] Values are means of three replications, standard deviation is given in parentheses.

(MIC: 250 ppm). Ueki group examined the antibiotic activity of UK-3A in 1997, and found that UK-3A did not show antibiotic activity against *E. coli*, *B. subtilis* and *S. aureus*, but indicated antibiotic activity against *C. albicans*.[3] These results revealed that AD-3 which contains a longer aliphatic chain (octanoyl group), apparently more active as a growth inhibitor of *B. subtilis* and *S. aureus* compare to **AD-1**, **AD-2**, Antimycin A_3 and the original compound UK-3A.

Brine Shrimp Lethality Test (BSLT) on *Artemia salina* provided by Meyer[10] was a convenient probe for preliminary assessment of the toxicity level of 2-hydroxynicotinoyl-serine-butyl esters. The measure of toxicity is reflected by LC_{50}. LC_{50} value greater than 30 ppm for tested samples were considered inactive (non-toxic).[10,11] As shown in Table 2, **AD-1**, **AD-2** and **AD-3** have LC_{50} values over 30 ppm, so they were assigned as non-toxic compounds. The highest potency to cause toxicity in *A. salina* was displayed by **AD-2** (LC_{50}: 266.83 ppm), which resulted in 100% shrimp death at a concentration of 1000 ppm. It was presumed that the presence of an aromatic ring (phenyl moiety) on the side chain of **AD-2** caused an increase in its toxicity level. **AD-1** (LC_{50}: 811.01) displayed lower toxicity level than **AD-2**, and **AD-3** (LC_{50}: 3620.41 ppm) indicated the lowest toxicity. Based on these results, **AD-3**, which had the lowest potency to cause the toxicity in *A. salina* and also showed antibiotic activity, should be considered and developed as a new synthetic antibiotic that selectively inhibits *B. subtilis* and *S. aureus* growth.

In conclusion, we have synthesized novel 2-hydroxynicotinoyl-serine-butyl esters through three-step reactions afforded **AD-1**, **AD-2** and **AD-3**. Among them, **AD-3** indicated the lowest potency to cause the toxicity in *A. salina* and showed greater activity as a growth inhibitor of *B. subtilis* and *S. aureus* compared to Antimycin A_3.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2010.05.104.

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