POTENT INHIBITORY EFFECT OF ANTIBIOTIC 1233A ON CHOLESTEROL BIOSYNTHESIS WHICH SPECIFICALLY BLOCKS 3-HYDROXY-3-METHYLGLUTARYL COENZYME A SYNTHASE

Sir:

During the course of screening for physiologically active metabolites from microorganisms a β-lactone was detected from *Scopulariopsis* sp. and *Fusarium* sp. which inhibited cholesterogenesis and was also a potent, specific inhibitor of the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) synthase. This compound was found to be identical to 1233A (**1**), an antimicrobial β-lactone isolated from *Cephalosporium*.[1] The effect of 1233A on HMG-CoA synthase and cholesterol biosynthesis is described in this communication.

The activity of cholesterol synthesis was measured by the incorporation of [^{14}C]acetate or [^{14}C]mevalonate into the non-saponifiable fraction of a rat liver enzyme system according to the method described by KURODA and ENDO.[2] The [^{14}C]acetate incorporation was 50% inhibited by 0.58 μg/ml of 1233A. On the other hand, the [^{14}C]mevalonate incorporation was not affected. It was suggested that the inhibition site of 1233A lies within steps between acetate and mevalonate. Therefore, the effects of 1233A on enzymes involved in mevalonate synthesis, HMG-CoA reductase, HMG-CoA synthase and acetoacetyl-CoA thiolase were investigated by the methods previously reported.[3~5] As summarized in Table 1 (Expt 1 and Expt 2), the IC_{50} for 1233A with HMG-CoA synthase was 0.032~0.065 μg/ml. However, the activity of HMG-CoA reductase and acetoacetyl-CoA thiolase was not affected by the compound at 40~50 μg/ml. Under the same conditions compactin (ML-236B) and lovastatin (mevinolin) specifically inhibited HMG-CoA reductase as reported by ENDO[6] and ALBERTS *et al.*[7] The results demonstrate that 1233A is a potent specific inhibitor of HMG-CoA synthase and cholesterol synthesis in the cell free rat liver system and to our knowledge this is the first report of a specific inhibitor of this enzyme.

The taxonomy of the producing organisms, production, isolation and biochemical and biological properties of this compound will be described in future publications.

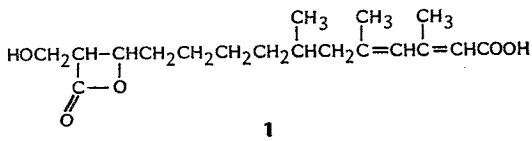

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Table 1. The effects of 1233A on the incorporation of [^{14}C]acetate and [^{14}C]mevalonate into non-saponifiable fraction, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, HMG-CoA synthase and acetoacetyl-CoA thiolase.

Inhibitor	IC_{50} (μg/ml)				
	[^{14}C]Acetate incorporation	[^{14}C]Mevalonate incorporation	HMG-CoA reductase	HMG-CoA synthase	Acetoacetyl-CoA thiolase
Expt 1					
1233A	0.58	>50	>50	0.065	>50
Compactin (ML-236B)	0.0024	ND	0.018	>50	>50
Expt 2					
1233A	ND	ND	>40	0.032	>40
Lovastatin (Mevinolin) (Open acid)	ND	ND	0.001	>80	ND

ND: Not done.

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