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Novel substances of marine origin as drug metabolism inhibitors

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Several compounds and fractions from the extracts of marine invertebrates have been found to possess cardiovascular, central nervous system and anticancer activities (Kaul, 1972; Kaul, Kulkarni & others, 1977; Schmitz, Campbell & others, 1977). The extracts of one of the marine organisms, *Aplysia dactylomela*, commonly known as sea hare, potentiated the pentobarbitone induced sleep-time in mice. The bioassay guided fractionation of this extract led to the isolation of dactylyne (I), a dibromochloro cyclic ether which was the active principle responsible for the potentiation (Kaul, Kulkarni & others, 1978). Several other halogenated cyclic ethers (II–V) have also been found in the algae of *Laurencia* genus (Irie, Suzuki, Masamune, 1968; Irie, Izawa & Kurosawa, 1970; Fukuzawa, Kurosawa & Irie, 1972). We now report that laureatin (II), isolaureatin (III) and laurefucin (IV) isolated from the red alga *Laurencia nipponica* and laurencin (V) from *L. glandulifera* also prolong the pentobarbitone

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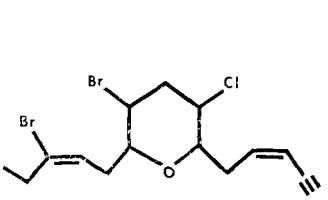
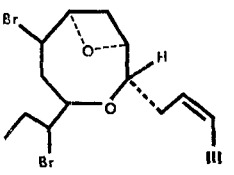
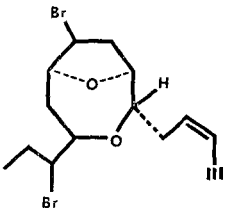


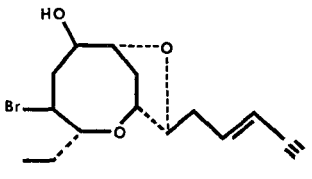
Dactylyne
(I)



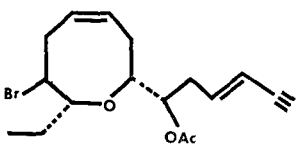
Laureatin
(II)



Isolaureatin
(III)



Laurefucin
(IV)



Laurencin
(V)

induced sleep-time. Based on the evidence obtained, it appears that this group of marine derived subtances acts by inhibiting the metabolism of pentobarbitone.

Male Swiss mice (ICRf: Sprague Dawley), 20–25 g, were maintained on a 12 h light/dark cycle with free access to food and water. Groups of 6–10 mice each were used per treatment. All marine substances, dissolved in dimethylsulphoxide (0·1 ml) and made up to volume with distilled water, were injected (10 mg kg^{-1}, i.p.) 30 min before pentobarbitone sodium administration (60 mg kg^{-1}, i.p.) The control group received an appropriate volume of saline, followed by the barbiturate dose. The onset and the duration of sleep were noted in all animals. A modified assay of Hollister, Kanter & Clyde (1963) was used to determine the blood concentrations of pentobarbitone in order to examine the relation of these concentrations with the duration of sleep-time.

Table 1 summarizes the effects of the compounds I–V on the pentobarbitone induced sleep-time. All compounds prolonged the sleep-time significantly ($P < 0.001$), dactylyne being the most potent. Among the laurencia group, isolaureatin was the most potent. Therefore, these two compounds were studied further in order to correlate the duration of sleep with the blood concentrations of pentobarbitone in mice pretreated with the compounds. The blood concentrations at 1 h, at which time the control mice recovered from sleep, were significantly ($P < 0.001$) higher in the dactylyne and isolaureatin pretreated mice than the saline pretreated controls. However, the concentrations at the time of awakening were nearly the same in all groups, the dactylyne and isolaureatin groups having slept several hours longer than the control group. Dactylyne shows this effect on metabolic elimination by both intraperitoneal and intravenous routes. These data suggest that both dactylyne and isolaureatin inhibit the metabolic elimination of pentobarbitone in mice. The other possibility would have been an effect of these compounds on the kidney function, but pentobarbitone is known to be excreted in urine only to a minor extent (Ossenberg, Peignoux & others, 1975).

Table 1. *Effect of various halogenated and acetylenic cyclic ethers on pentobarbitone* (60 *mg* kg^{-1}, *i.p.*) *induced sleep-time and blood concentrations in mice.*

Compounds	n	Sleep-time (min with s.d.)	Pentobarbitone blood concns ($\mu g\ ml^{-1}$) at 1 h	on awaking
Control	10	62 s.d. 19·1	16·9 s.d. 0·5	15·2 s.d. 2·5
Dactylyne	10	215 s.d. 25·2 ($P < 0.001$)	27·1 s.d. 2·3 ($P < 0.001$)	15.3 s.d. 1·6
Laureatin	6	142 s.d. 29·5 ($P < 0.001$)		
Isolaureatin	6	173 s.d. 47 ($P < 0.001$)	23·1 s.d. 1·3 ($P < 0.001$)	15·2 s.d. 1·4
Laurefucin	6	78 s.d. 13·4 ($P < 0.05$)		
Laurencin	6	120 s.d. 18·1 ($P < 0.001$)		

Our earlier studies had indicated that dactylyne is devoid of any direct pharmacological property of its own (Kaul, Kulkarni & Schmitz, 1977). Preliminary gross behavioural studies have shown that laureatin, isolaureatin, laurefucin and laurencin also have little or no pharmacological activity of their own at the doses used in these studies. Thus, these halogenated and acetylenic cyclic ethers of marine origin constitute a novel group of drug metabolism inhibitors. It is interesting that dactylyne has a much wider safety margin (non-lethal up to 200 mg kg^{-1}, i.v.) than the well known inhibitor SKF 525A (LD50 = 60 mg kg^{-1}). A preliminary sub-acute toxicity study revealed no gross morphological and histological lesions in the vital organs of mice treated with dactylyne for 15 days (Kaul & Kulkarni, 1978).

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