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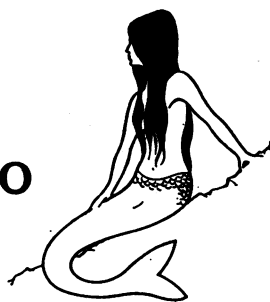
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A major theme throughout this book is the development of functional capacity and the degree of autonomy of various fetal endocrine mechanisms. Data from the human, and from the experimental animal are compared and contrasted making this a book for clinicians and advanced medical students as well as for research workers in the various disciplines of reproductive physiology.

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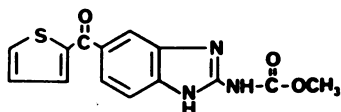
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Nocodazole

A New Synthetic Microtubule Inhibitor



Nocodazole {methyl [5-(2-thienylcarbonyl)-1H-benzimidazol-2-yl]carbamate, R17934} is a new synthetic microtubule inhibitor, chemically unrelated to the microtubule-disintegrating alkaloids colchicine, the vinca alkaloids, rotenone and podophyllotoxin. Investigation into the mechanism of its activity against experimental neoplasms^{1,2} revealed that the compound exhibited highly specific antimicrotubular activity, inducing the total disappearance of microtubules from neoplastic cells *in vivo*³ and from mammalian cells in culture.⁴ This activity and the ensuing cell-biological effects were identical to those produced by the antimicrotubular alkaloids. Effects include:

- 1) loss of directional cell movement⁴
- 2) alteration of cell shape⁴
- 3) loss of ordered subcellular organelle movements⁴
- 4) randomization of subcellular organelle topography^{3,4,5}
- 5) inhibition of insulin secretion⁶
- 6) induction of Con-A cap formation on human polymorphonuclear leukocytes⁷
- 7) appearance of bundles of 10nm-filaments and annulate lamellae^{3,4,8,9}
- 9) destruction of the mitotic spindle with ensuing mitotic block.^{3,4,10}

The high degree of specificity was demonstrated by the absence of nonspecific side effects unrelated to its antimicrotubular properties.^{3,4} The cell-biological effects were identical within a large dose range (0.04-100 μ g/ml), and concentrations that had no effect on microtubules (<0.01 μ g/ml) showed no effects whatsoever on cellular structure, behavior, growth or viability.⁴ The antimicrotubular activity in tissue-cultured cells was almost immediately visible and reversible.

Subsequently, it was shown that **Nocodazole** inhibited the polymerization of tubulin *in vitro* in a dose-dependent way and that it shared the same binding site on the tubulin molecule with colchicine.¹¹ In contrast to colchicine, however, **Nocodazole** is easily removed from its binding site.¹¹

Comparison of its effects with those of colchicine should help establish the involvement of tubulin and microtubules in the studied phenomena. Colchicine-induced alterations unrelated to interaction with tubulin have indeed been reported!^{2,13} The rapid penetration of **Nocodazole** and the lack of irreversible binding should facilitate short-term experiments, especially when phenomena related to the reappearance of microtubules are studied. The reversibility of its action can also be favorably exploited when cell synchronization is attempted through a reversible mitotic block.

A number of organisms that are relatively resistant to the action of colchicine could prove sensitive to **Nocodazole**. Preliminary data indicates, for instance, that **Nocodazole** shows antimicrotubular effects in fungi.¹⁴

The compound is stable in biological media for at least 7 days.

Thus, the availability of a synthetic compound with a simple chemical structure unrelated to the plant alkaloids and with a specific antimicrotubular activity is potentially useful in the field of microtubule research.

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