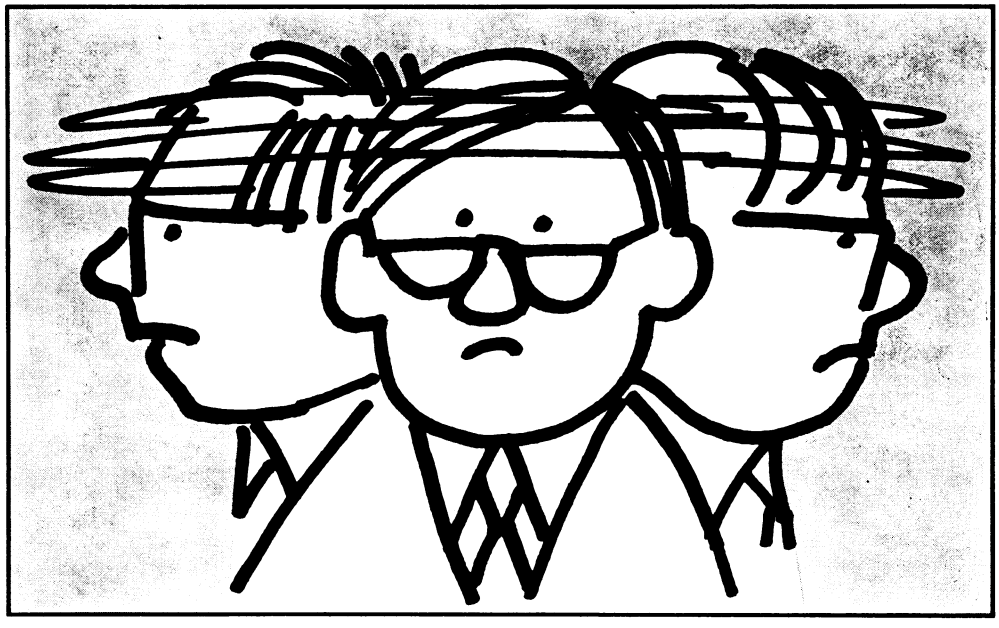

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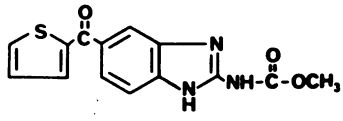
Nocodazole

A New Synthetic Microtubule Inhibitor



Nocodazole {methyl [5-(2-thienylcarbonyl)-1*H*-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 movement[4]
2) alteration of cell shape[4]
3) loss of ordered subcellular organelle movements[4]
4) randomization of subcellular organelle topography[3,4,5]
5) inhibition of insulin secretion[6]
6) induction of Con-A cap formation on human polymorphonuclear leukocytes[7]
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 (0.04-100μg/ml), and concentrations that had no effect on microtubules (<0.01 μg/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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