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JOHANNESBURG

FACULTY OF MEDICINE

PROFESSOR OF MEDICAL BIOCHEMISTRY

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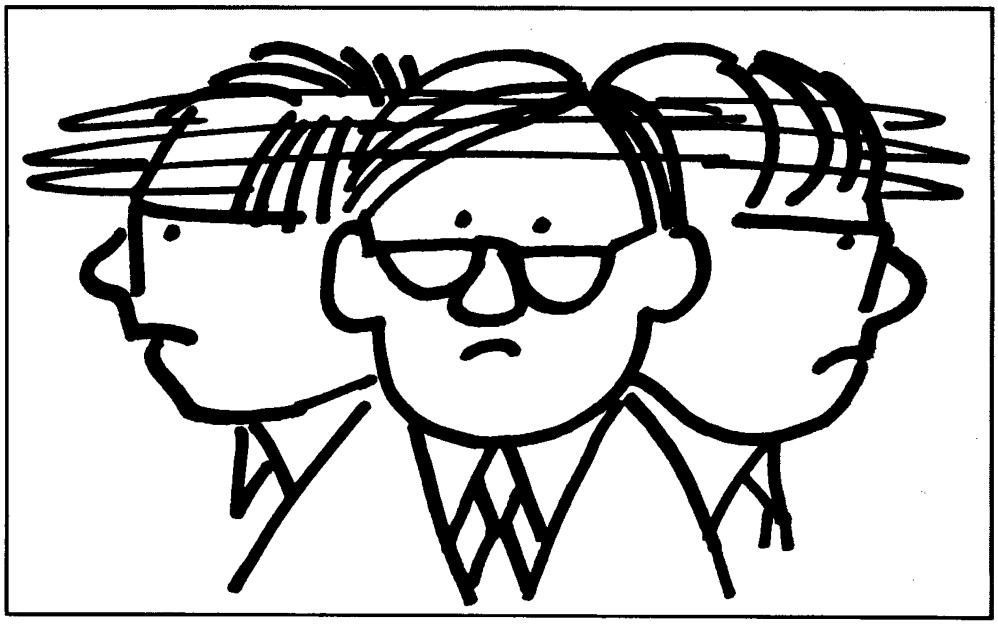

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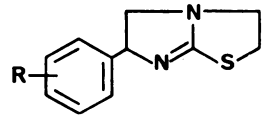
Levamisole and analogs: a class of potent alkaline phosphatase inhibitors



R = H (Tetramisole, Levamisole)
R = *m*-Br (R 8231)
R = *p*-Br (*l*-*p*-Bromotetramisole, *d*-*p*-Bromotetramisole)

Tetramisole (R 8299, *dl*-2,3,5,6-tetrahydro-6-phenylimidazo[2,1-*b*]thiazole hydrochloride) is a potent, broad-spectrum anthelmintic, which exhibits high activity against several species of gastrointestinal and pulmonary nematodes, without undesirable side effects such as antihistaminic, anticholinergic and adrenolytic activities.[1]

In further evaluating the biochemical effects of **Tetramisole**, it was discovered that the compound was a potent inhibitor of alkaline phosphatase.[2] Consequently, similar studies were undertaken on analogs of **Tetramisole**. Its levorotatory isomer, **Levamisole** (R 12456, *l*-tetramisole, *l*-2,3,5,6-tetrahydro-6-phenylimidazo[2,1-*b*]thiazole hydrochloride)[2-4] and R 8231 [*dl*-6-(*m*-bromophenyl)-2,3,5,6-tetrahydroimidazo[2,1-*b*]thiazole oxalate][2-4] were found to be potent, stereospecific, noncompetitive inhibitors of alkaline phosphatase from various tissues from the dog and the rat, yet showed no inhibition of the intestinal isoenzyme. The *d*-isomers were completely inactive.[2-4] ***l*-*p*-Bromotetramisole** (R 30402, *p*-bromolevamisole) proved to be more potent than **Levamisole** in its inhibition of alkaline phosphatase.[5,6] The inactive *d*-isomer, ***d*-*p*-bromotetramisole** (R 30402), is useful as an internal control.[6]

The organo- and stereospecificities of these inhibitors were demonstrated both biochemically and cytochemically in a variety of tissues and species.[2-4,7-10] Specific phosphatase activities are not altered by these compounds.[4,6] Thus, this high degree of specificity has enabled the differentiation between "true" 5'-nucleotidase, Na-K-ATPase, Mg-ATPase or glucose-6-phosphatase and nonspecific alkaline phosphatase, the latter being totally suppressed upon addition of inhibitor.[4,6,11-16]

Levamisole has been used as an inhibitor in studies of the organ source of human serum alkaline phosphatases.[8] At 0.1m*M*, the compound noncompetitively inhibited liver and intestinal "A" isoenzymes; heat-stable isoenzymes (placental, Regan, "unmasked" and intestinal "B") were found to be resistant.[8] The presence of the Regan isoenzyme is of potential diagnostic importance.[17] The kinetics of inhibition of purified human alkaline phosphatase isoenzymes by **Levamisole** have been described.[18]

***l*-*p*-Bromotetramisole** has been reported recently to be an effective reagent for the quantitative determination of intestinal and placental alkaline phosphatase isoenzymes in human serum.[19]

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