PROBING RECEPTORS WITH NATURAL AND SYNTHETIC ALKALOIDS

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The four phenolic 6-keto-N-methylmorphinans, their O-methyl ethers and the aromatic unsubstituted 6-keto-N-methylmorphinan have been synthesized to evaluate the effect of aromatic substitution on analgesic potency and binding to opiate receptors [H. Schmidhammer, A. E. Jacobson and A. Brossi, Med. Res. Reviews, 3, 1 (1983)]. The data obtained revealed interesting relationships which will stimulate structural modifications through molecular modeling.

Synthetic perhydrohistrionicotoxins have been made available in their optically active natural and unnatural forms [K. Takahashi, B. Witkop, A. Brossi, M. A. Maleque and E. X. Albuquerque, Helv. Chim. Acta, 65, 252 (1982)], and their evaluation by refined electrophysiological techniques is in progress. New interest has emerged in the "naked" perhydrohistrionicotoxins, their diastereomers and optical antipodes, now readily available by stereoselective methods (W. Gessner, K. Takahashi, B. Witkop and A. Brossi, unpublished results).

Natural 3-demethylcolchicine binds well to tubulin, is quite toxic to mice and has substantial activity in the lymphocytic leukemia P388 screen. The unnatural 1-demethyl analog prepared from colchicine [M. Rösner, H. G. Capraro, M. A. Iorio, A. E. Jacobson, L. Atwell, A. Brossi, T. Williams, R. H. Sik and C. F. Chignell, J. Med. Chem. 24, 257 (1981)] was found to be considerably less active biologically. An X-ray comparision of the two phenolic tropolones in the solid state revealed significant differences in their hydrogen bonding behavior, suggesting that the latter might be of consequence for tubulin binding and polymerization (A. Brossi, P. N. Sharma and J. V. Silverton, unpublished results). Affinity labeling of colchifoline and deacetylcolchicine with fluorescindiacetate and spin-labels afforded derivatives useful for probing the colchicine binding site on tubulin (P. N. Sharma, A. Brossi, J. V. Silverton and C. F. Chignell, 185th ACS-Meeting in Seattle, March 1983, Div. of Med. Chem., Abstr. No. 83).