COMPUTER-ASSISTED STRUCTURE ANTITUMOR ACTIVITY ANALYSIS OF PURINES, PURINE NUCLEOSIDES AND THEIR AZA AND DEAZA ANALOGS

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We have undertaken a comprehensive computer-assisted structure anticancer activity analysis of 5,000 purines and 16,000 compounds with purine-like frameworks of carbon and nitrogen that have been evaluated at the National Cancer Institute (NCI). This study takes advantage of the computer's ability to search substructures according to precise definitions and to manipulate these substructures utilizing Boolean logic. For the analysis, compounds were categorized into logical structural types and evaluated to provide the following information. 1) The number of compounds tested under each category in any in vivo or in vitro test system. 2) The number of compounds tested in vivo against i.p. implanted murine P388 lymphocytic leukemia and L1210 lymphoid leukemia. 3) The number of compounds currently considered to have "confirmed" activity against either P388 or L1210 leukemia. 4) The percentage of comfirmed actives that can be anticipated upon completion of the testing.

The results of the study are summarized below: 1) Purines substituted at the 7-nitrogen position (780 compounds) are inactive in all the in vivo and in vitro test systems. 2) The replacement of the ribose at the 9-position in purine nucleosides by a glucose moiety completely abolishes the activity in both P388 and L1210 leukemias. 3) Contrary to the general impression, purines as a class show better activity in P388 than in L1210 leukemia. 4) 6-Mercaptopurine nucleosides, on the other hand, show far better activity in L1210 leukemia than in P388 while 6 mercaptoguanines show good activity in both P388 and L1210. 5) For the majority of the aza and deazapurine analogs, the presence of ribose is the most important factor in conferring antitumor activity. 6) Several interesting classes of purines and their aza and deaza analogs, e.g. pyrazolo [3,4-c] pyridazines and pyrazolo-[4,3-c] pyridazines are not well represented and are worthy of further investigation. The implications of these and other findings to future research will be discussed.