# SYNTHESIS AND ANTITUMOR STUDIES OF HYDRAZONES DERIVED FROM MONOSUBSTITUED 2-ACETYLPYRIDINES AND 2-HYDRAZINO-1-METHYLBENZIMIDAZOLE:

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In the course of the development of novel hydrazones as potential antitumor agents, we have found that 1-methyl-2-benzimidazolyl hydrazone derived from 2-acetylpyridine (compound EPH 116) exhibits potent cytotoxic activity ($IC_{50}$ = 0.004-0.018 μM) *in vitro* against a pannel of human tumor cell lines. [1] EPH 116 was also found to be a potent inducer of apoptosis in Burkitt´s lymphoma cells compared to camptothecin. Furthermore, EPH 116 inhibited the growth of CXF 280 colon tumor xenografts in nude mice in a dose dependent manner. In view of this promising antitumor activity we have synthesized several analogues of EPH 116 in which various positions of the 2-acetylpyridine ring is substituted by electron withdrawing or donating groups. The antiproliferative activities of these agents were studied in a pannel of human tumor cell lines (Burkitt´s lymphoma, Hela cervix carcinoma, HT-29 colon carcinoma, hydroxyurea-resistant and multidrug resistant KB cell lines). The activities were compared to that of EPH 116. The following conclusions could be drawn: i) All the compounds are potent inhibitors of the proliferation of Burkitt´s lymphoma cells ($IC_{50}$ = 0.001-2.02 μM). ii) 2-Acetylpyridines bearing electron donating substituents are highly cytotoxic to HeLa ($IC_{50}$ = 0.0003-0.183 μM) and HT-29 ($IC_{50}$ = 0.003-0.14 μM) cells compared to those bearing electron withdrawing groups ($IC_{50}$ = 0.165-17.56 μM). The 6-methyl-2-acetylpyridine analogue EPH 135 inhibited the growth (60%) of HTB 1773 cells transplanted in nude CD1 mice at doses of 60 mg/kg/b. wt. However due to problems of solubility, a MTD was not reached.
In Burkitt´s lymphoma cells, two-fold $IC_{50}$-concentrations of two novel hydrazones derived from 2-acetyl-6-phenyl-pyridine (EPH 355) and 2-acetyl-4-dimethylaminopyridine (EPH 362) induced 60 and 81 % apoptosis respectively. On the contrary, two-fold $IC_{50}$-concentrations of hydroxyurea and camptothecin induced 6.5 and 10 % of apoptosis respectively. The synthesis and structure-activity relationships of this class of novel antitumor agents will be presented.
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[1] Easmon, J., Pürstinger, G., Roth, T., Fiebig, H-H., Marcel, J., Jaeger, W., Heinisch, G., Hofmann, J., *Int. J. Cancer*: **9**, 89-96 (2001).