# PREPARATION OF SOME ARYLHYDRAZONES OF MANNICH BASES DESIGNED AS CYTOTOXIC AGENTS

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Kavitha Advikolanu, M.Sc.

Saskatoon, Saskatchewan

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Dedicated

To

Mummy, Daddy

and

Kiran

## ABSTRACT

Alkylating agents represent a class of chemotherapeutic anticancer agents used in the treatment of cancer. A large number of alkylating agents have been synthesized and several of them are in clinical use today. In an attempt to develop drugs to combat the disease, it has become increasingly important to synthesize new agents based on rational design along with systematic strategies and advances in biology. The fundamental requirement of an anticancer agent would be the selective susceptibility of the tumor to the agent's cytotoxic action.

Mannich bases have a broad spectrum of activity and earlier work from these laboratories has demonstrated the antineoplastic activity of these compounds. Mannich bases were synthesized by varying the substituent pattern in the $\alpha$ and $\alpha'$ positions to the carbonyl group and their corresponding arylhydrazones in order to determine the cytotoxic activity of these compounds. Variation in the substituents in the aryl ring in the hydrazones of the following two series of compounds was carried out: namely 1-aryl-3-dimethylamino-1-propanone hydrochloride (II) and 1-aryl-5-dimethylamino-1-penten-3-one hydrochloride (IIIa) and examined as candidate cytotoxic agents.

The Human Tumor Colony Forming Assay, the KB screen and L1210 cytotoxic assay was undertaken on some of the compounds. In the in vitro Human Tumor Colony Forming Assay two

concentrations of compounds were used namely 100 and 10$\mu$M and it was found that the compounds were cytotoxic to the cells at 100$\mu$M (except for 1-phenyl-4,4,-dimethyl,-5-dimethylamino-1-penten-3-one phenylhydrazone hydrochloride). In the KB screen some of the Mannich bases and the corresponding phenylhydrazones were studied for their cytotoxic action. Compound 1-phenyl-4,4,-dimethyl,-5-1dimethylamino-1-penten-3-one hydrochloride was active in this assay having an $ED_{50}$ value of 2.63$\mu$g/ml (the criteria for activity is 50% inhibition of KB cell replication by 4$\mu$g/ml or less of the compound). The in vitro results obtained in the L1210 assay indicated that all the compounds were less active than melphalan, the reference antineoplastic drug ($ED_{50}$ = 0.12$\mu$M). The most active Mannich base IIIa had an $ED_{50}$ value of 5.1$\mu$M and among the arylhydrazones, 1-phenyl-3-dimethylamino-1-propanone 4-nitro phenylhydrazone hydrochloride was the most active derivative with an $ED_{50}$ value of 4.9$\mu$M. The melting temperature studies on some of the compounds, however, did not show that these compounds bound with calf-thymus DNA, poly d(A-T) and, therefore, it may be inferred that intercalation may be only a minor cause of cytotoxic action of active compounds. Under the NCI'S Developmental Therapeutic Program the compounds were studied for anti-HIV activity using the XTT tetrazolium assay. 1-phenyl-5-dimethylamino-1-penten-3-one pentafluorophenyl hydrazone hydrochloride in the series of arylhydrazones prepared was found to be the most active to the

infected cells at $8.60 \times 10^{-8}$ M with an $IC_{50}$ value of $>8.57 \times 10^{-5}$ M followed by compound 1-phenyl-5-dimethylamino-1-penten-3-one-2,4-dichloro phenylhydrazone hydrochloride with an $IC_{50}$ value of $>9.02 \times 10^{-6}$ and an $EC_{50}$ value of approximately 20%. The structure of compound X was studied by the X-ray crystallographic technique.