P013 SYNTHESIS AND ANTITUMOR ACTIVITY OF BIS-PLATINUM COMPLEXES VARYING IN THE NATURE OF THE BRIDGING DIAMINE LINKER GROUP.

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Bisplatinum complexes are a promising new class of structurally unique dimeric antitumor agents [1] exhibiting novel DNA binding properties [2]. In the interest of elucidating key structure-activity relationships (SAR), and thus identifying optimally active complexes, substituted bisplatinum complexes of the generic structure (Figure) were synthesized and evaluated in sensitive and platinum(Pt)-resistant cell lines *in vitro* (L1210, P388) and *in vivo* (L1210):

$$X_2(A)PtNH_2\text{-}L\text{-}NH_2Pt(A)X_2 \qquad \mathbf{1}$$

In **1**, L represents a straight-chain or functionalized hydrocarbon moiety (linker group) having a linker length (n) of 4 to 6 atoms; X (or X_2) represents chloride or malonate leaving groups, and A is either NH_3 or $EtNH_2$. In principle, varying L allows one to modify the physical and structural properties of **1**, as relates to enhanced specificity and affinity of DNA binding as well as to optimal aqueous solubility. Nine categories of complexes can be identified based on the organic nature of the linker group. Complexes were prepared by incorporating diamines into the following optimized bisplatinum synthetic scheme:

$$2K[PtACl_3],\ 2 \xrightarrow{6\ KI} [2K[PtAI_3]] \xrightarrow{H_2N\text{–}L\text{–}NH_2} \mathbf{1}\ (X = I) \quad (1)$$

$$\mathbf{1} + 4\ AgNO_3 \longrightarrow \mathbf{1}\ (X = H_2O) \xrightarrow{Na(H)Cl} \mathbf{1}\ (X = Cl) \quad (2a)$$

$$\mathbf{1} + 2\ Ag_2C_3H_2O_4\ (s) \longrightarrow \mathbf{1}\ (X_2 = \text{malonate}) \quad (2b)$$

Antitumor testing and SAR data indicate that (1) significant activity was observed *in vivo* in L1210 leukemia, Colon 26 carcinoma, and to a lesser extent, in AH 125 non-small cell lung carcinoma; (2) activity is curative for the parent system (L= $-(CH_2)_5-$, X=Cl) and the analog, L= $-(CH_2)_6-$, X_2= malonate; (3) monoalkylsubstitution (n = 5,6) and monosubstitution in the 3-position (n= 5) appear to be optimal. More specifically, the potency of the 3-hydroxy analog is approximately 10x higher than that of the complex $[Pt(DACH)Cl_2]$; and (4) monoalkyl substitution leads to comparable potency but higher resistance factors relative to the parent system.

1. N.P Farrell, S.G. de Almeida, and K.A. Skov, *J. Am. Chem. Soc.*, **110**, *5018* (1988).
2. J.D. Robert, B. Van Houten, Y. Qu, and N.P. Farrell, *Nuc. Acids Res.*, **17**, *9719-9733* (1989).