STUDIES ON TUMOUR ACTIVE COMPOUNDS WITH MULTIPLE METAL CENTRES

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DECLARATION

I, the author of the thesis, declare that none of the material in this thesis has been previously submitted by me or any other candidate for any degree to this or any other university.

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ABSTRACT

Four tumour active trinuclear complexes: DH4Cl: [{*trans*-$PtCl(NH_3)_2$}$_2$*m*-{*trans*-$Pd(NH_3)_2(H_2N(CH_2)_4NH_2)_2$]$Cl_4$, DH5Cl: [{*trans*-$PtCl(NH_3)_2$}$_2$*m*-{*trans*-$Pd(NH_3)_2(H_2N(CH_2)_5NH_2)_2$]$Cl_4$, DH6Cl: [{*trans*-$PtCl(NH_3)_2$}$_2$*m*-{*trans*-$Pd(NH_3)_2(H_2N(CH_2)_6NH_2)_2$]$Cl_4$, DH7Cl: [{*trans*-$PtCl(NH_3)_2$}$_2$*m*-{*trans*-$Pd(NH_3)_2$-$(H_2N(CH_2)_7NH_2)_2$]$Cl_4$ and one dinuclear complex DHD: [{*trans*-$PtCl(NH_3)_2$}*m*-{$H_2N(CH_2)_6NH_2$}{*trans*-$PdCl(NH_3)_2$]$Cl(NO_3)$, have been prepared and characterised based on elemental analyses, IR, Raman, mass and ^{1}H NMR spectral measurements. For the trinuclear complexes, the synthesis has been carried out using a step-up method branching out from the central palladium unit. A purity of about 95% has been obtained by repeated dissolution and precipitation. The activity against human cancer cell lines including ovary cell lines: A2780, A2780^{cisR}, A2780^{ZD0473R}, non small lung cell line: NCI-H640 and melanoma: Me-10538 have been determined based on MMT assay. Cell uptakes, DNA-binding have been determined for ovary cell lines: A2780, A2780^{cisR}. The nature of interaction with pBR322 plasmid DNA and ssDNA has been studied for trinuclear complexes DH4Cl, DH5Cl, DH6Cl and DH7Cl and the dinuclear complex DHD. Interaction of DH6Cl with adenine and guanine has also been studied by HPLC. The compounds are found to exhibit significant anticancer activity against cancer cell lines especially ovarian cancer cell lines: A2780, A2780^{cisR} and A2780^{ZD0473R}. DH6Cl in which the linking diamine has six carbon atoms is found to be the most active compound. As the number of carbon atoms in the

linking diamine is changed from the optimum value of six, the activity is found to decrease, illustrating the structure-activity relationship. The increase in uptake of the trinuclear complexes in A2780 cell line with the increase in size of the linking diamine coupled with the low molar conductivity values found for the solutions of the compounds suggest that the compounds would remain in solution as undissociated 'molecules' and hence could cross the cell membrane by passive diffusion. Much lower resistance factors for the all the multinuclear compounds including DHD as applied to $A2780^{cisR}$ cell line, as compared to that for cisplatin, suggest that the compounds are able to overcome multiple mechanisms of resistance operating in the cell line. All of the multinuclear complexes are expected to form long-range interstrand GG adducts with DNA, causing irreversible global changes in the DNA conformation but unlike cisplatin do not cause sufficient DNA bending to be recognized by HMG 1 protein. Increasing prevention of BamH1 digestion with the increase in concentration of the multinuclear compounds also provide support to the idea that the compounds because of the formation of a plethora of interstrand GG adducts are able to cause irreversible changes in DNA conformation. The results of the study show that indeed new trinuclear tumour active compounds can be found by replacing the central platinum unit in BBR3464 with other suitable metal units.

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ABBREVIATIONS

TMN	TMN system, TMN stands for Tumour, Nodes and Metastases
DNA	Deoxyribonucleic acid
Cis-DDP	*cis*-diamminedichloroplatinum(II) also called cisplatin
Trans-DDP	*trans*-diamminedichloroplatinum(II) also called transplatin
GSH:	Glutathione
MT:	Metallothionine
HMG:	High mobility group
MMR:	Mismatch repair
DACH:	1,2-diaminocyclohexane
CBCD	*cis*-diammine-1,1-cyclobutanedicarboxylateplatinum(II), also called carboplatin
JM	Johnson Matthey
ICR	Institute of Cancer Research
JM216	bis(acetato)ammine-dichloro(cyclohexylamine)platinum(IV)
JM335	*trans*-ammine(cyclohexylaminedichloro-dihydroxo)platinum(IV)
ZD0473	*cis*-amminedichloro(2-methylpyridine)platinum(II)
BBR3464	$[\{trans\text{-}PtCl(NH_3)_2\}_2\{\mu\text{-}trans\text{-}Pt(NH_3)_2(NH_2(CH_2)_6NH_2)_2\}]^{4+}$
DH4Cl	$[\{trans\text{-}PtCl(NH_3)_2\}_2\{\mu\text{-}trans\text{-}Pd(NH_3)_2\text{-}(H_2N(CH_2)_4NH_2)_2]Cl_4$
DH5Cl	$[\{trans\text{-}PtCl(NH_3)_2\}_2\{\mu\text{-}trans\text{-}Pd(NH_3)_2\text{-}(H_2N(CH_2)_5NH_2)_2]Cl_4$
DH6Cl	$[\{trans\text{-}PtCl(NH_3)_2\}_2\{\mu\text{-}trans\text{-}Pd(NH_3)_2\text{-}(H_2N(CH_2)_6NH_2)_2]Cl_4$
DH7Cl	$[\{trans\text{-}PtCl(NH_3)_2\}_2\{\mu\text{-}trans\text{-}Pd(NH_3)_2\text{-}(H_2N(CH_2)_7NH_2)_2]Cl_4$
DHD	$[\{trans\text{-}PtCl(NH_3)_2\}\{\mu\text{-}(H_2N(CH_2)_6NH_2)\}\{trans\text{-}PdCl(NH_3)_2]Cl(NO_3)$
DMF	Dimethyl formamide
DMSO	Dimethyl sulfoxide
Et_3N	Triethyl amine
EDTA	Ethylenediaminetetraacetic acid
dpzm	4,4'-dipyrazolylmethane

AAS	Atomic absorption spectrophotometry
IR	Infrared
NMR	Nuclear magnetic resonance
MTT	3-[4,5-dimethylthiazol-2yl]-diphenyl tetrazoliume bromide
FCS	Fetal calf serum
PBS	Phosphate buffered saline
Triton X-100	t-Octylphenooxypolyethoxyethanol
ssDNA	Salmon sperm DNA
AMP	Adonosine-5'-monophosphate
ri	Molar ratio
NB	Nucleobase
HPLC	High performance liquid chromatography
IC_{50} or ID_{50}	Concentration required to inhibit cell growth by 50% in cell culture
IC_{90}	Concentration required to inhibit cell growth by 90% in cell culture
RF	Resistant factor