Studies on new tumour active compounds with one or more metal centres

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Certification by the Supervisor

I certify that the thesis entitled: “Studies on new tumour active compounds with one or more metal centres” submitted by Hasan Tayyem for the Degree of Doctor of Philosophy of The University of Sydney is ready for examination.

Fazlul Huq

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.

Hasan Tayyem

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Contents

Abstract

The present study deals with the synthesis, characterization, determination of anticancer activity of three mononuclear *trans*-planaraminepalladium(II) complexes code named TH5, TH6 and TH7 and three trinuclear complexes code named TH1, TH8 and TH14. The activity of the compounds against human cancer cell lines: A2780, A2780^{cisR} and A2780^{ZD0473R}, cell uptake, DNA-binding and nature of interaction with pBR322 plasmid DNA have been determined. Whereas cisplatin binds with DNA forming mainly intrastrand GG adduct that causes local bending of a DNA strand, TH5, TH6, TH7, TH1 and TH8 bind with DNA forming mainly interstrand GG adducts that causes more of a global change in DNA conformation. Although TH5, TH6 and TH7 each have two substituted pyridine ligands in a *trans*-geometry (3-hydroxypyridine in TH5, 2-hydroxypyridine in TH6 and 4-hydroxypyridine in TH7), the compounds differ in their activity against ovarian cancer cell lines, indicating that non-covalent interactions involving the hydroxyl group may be playing a significant role in activity of the compounds. Among trinuclear complexes TH1 is found to be significantly more active than cisplatin. It is actually twice as active as cisplatin against the parent cell line A2780, thirteen times as active as cisplatin against the cisplatin-resistant cell line A2780^{cisR} and 11.5 times as active as cisplatin against the cell line A2780^{ZD0473R}. Whereas the resistance factor for cisplatin as applied to the cell lines A2780 and A2780^{cisR} cell lines is 12.9 that for TH1 is 1.98. The results suggest that TH1 has been able to significantly overcome resistance operating in A2780^{cisR} cell line. The compound is soluble in water so that it may be taken orally. Provided it has favourable toxicity profile, TH1 has the potential

to be developed into a highly active anticancer drug with a wider spectrum of activity than cisplatin. Although platinum drugs use a shot-gun approach to kill cancerous cells, widespread use in the clinic and increasing volume of their sale indicate that even in the genomic age, there is still need for shot-gun drugs in the clinic.

Abbreviations

AAS	Atomic absorption spectrophotometry
BBR3464	[{*trans*-$PtCl(NH_3)_2$}$_2${μ-*trans*-$Pt(NH_3)_2(NH_2(CH_2)_6NH_2)_2$}] $^{4+}$
C5-OHP-Cl	*trans*-bis(n-valerato)(1R,2R-cyclohexanediamine)(oxalate)platinum(IV)
CBCD	*cis*-diammine-1,1-cyclobutanedicarboxylateplatinum(II)
CDKs	Cyclin-dependent protein kinases
CH1	*trans*-PtCl2 (3-hydroxypyridine)2
cis-DDP	Cisplatin
DACH	1,2-diamminocyclohexane
DMF	*N,N*-dimethylformamide
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
DRA	Diffuse reflectance accessory
EDTA	Ethylenediaminetetraacetic acid
ESI	Electrospray ionization
FCS	Fetal calf serum
GSH	Glutathione
HNPCC	Hereditary nonpolyposis colorectal cancer
HPLC	High performance liquid chromatography
IC_{50}	Concentration required inhibiting cell growth by 50%
IR	Infrared
JM118	*cis*-amminedichloro(cyclohexaylamine)platinum(II)
JM216	bis-aceto-amminedichloro-cyclohexylammine-platinum(IV)
MMR	Mismatch repair
MT	Metallothionein
MTT	3-(4, 5-dimethylthiazol -2-yl)-2, 5-diphenyltetrazolium bromide
NER	Nucleotide excision repair
NMR	Nuclear magnetic resonance
NSCLC	Non-small cell lung cancer
PBS	Phosphate buffered saline
RF	Resistant factor
RNA	Ribonucleic acid

RPMI	Refers to media developed at Roswell Park Memorial Institute
SCLC	Small cell lung cancer
ssDNA	Salmon Sperm DNA
TAE	Tris-acetate EDTA
TBE	Tris-borate EDTA
TH1	[*trans*-$PtCl(NH_3)_2$]$_2${*trans*-Pt(3-hydroxypyridine)$_2$($H_2N(CH_2)_6NH_2)_2$]Cl_4
TH14	[*trans*-$PtCl(NH_3)_2$]$_2${*trans*-Pt(3-hydroxypyridine)$_2$($H_2N(CH_2)_4NH_2)_2$]Cl_4
TH5	*trans*-$PdCl_2$(3-hydroxypyridine)$_2$
TH6	*trans*-$PdCl_2$(2-hydroxypyridine)$_2$
TH7	*trans*-$PdCl_2$(4-hydroxypyridine)$_2$
TH8	[*trans*-$PtCl(NH_3)_2$]$_2${*trans*-Pd(4-hydroxypyridine)$_2$($H_2N(CH_2)_6NH_2)_2$]Cl_4
TPE	Tris-phosphate EDTA
trans-DDP	Transplatin
Triton X-100	t-Octylphenooxypolyethoxyethanol
ZD0473	*cis*-amminedichloro(2-methylpyridine)platinum(II)

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