南京大学
NANJING UNIVERSITY

Literature Report

Metal-based drug in Peter.J.Sadler's lab

Reporter: Zhu Mingli
Advisors: Prof. Zhao
Dr. Wei
20140407

Introducition of Peter.J.Sadler

- Prof. of *warwick universty*
- Member of *The Royal Society*
- Research Summary*:*

I. *Chemistry of metals in medicine*

II. *Design and chemical mechanism of action of therapeutic metal complexes(organometallic arene anticancer complexes, photoactivated metal anticancer complexes),metallomacrocycles as antivirals and stem-cell-mobilising agents*

III. *interactions with targets such as RNA, DNA and proteins*

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Review

Using coordination chemistry to design new medicines☆

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Diazido Mixed-Amine Platinum(IV) Anticancer Complexes Activatable by Visible-Light Form Novel DNA Adducts

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Journal of Medicinal Chemistry

ARTICLE

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Organometallic Half-Sandwich Iridium Anticancer Complexes

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CHEMISTRY
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FULL PAPER

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Mirror-Image Organometallic Osmium Arene Iminopyridine Halido Complexes Exhibit Similar Potent Anticancer Activity

Ying Fu,[a] Rina Soni,[a] María J. Romero,[a] Ana M. Pizarro,[a] Luca Salassa,[a, b] Guy J. Clarkson,[a] Jessica M. Hearn,[a, c] Abraha Habtemariam,[a] Martin Wills,[a] and Peter J. Sadler*[a]

Using coordination chemistry to design new medicines

- Contents:

I. Medicinal inorganic chemistry

II. Metallomacrocycles

III. Photoactivated platinum complexes

IV. Metal arene complexes

Medicinal inorganic chemistry

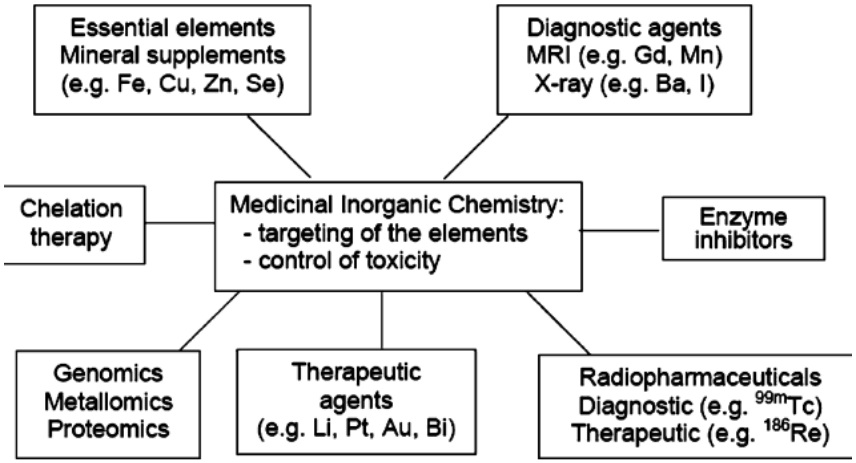


Fig. 1. Some of the areas of medicinal inorganic chemistry.

- Zinc is essential for life:catalytic or structural
- Selenium provides a good example of the importance of speciation

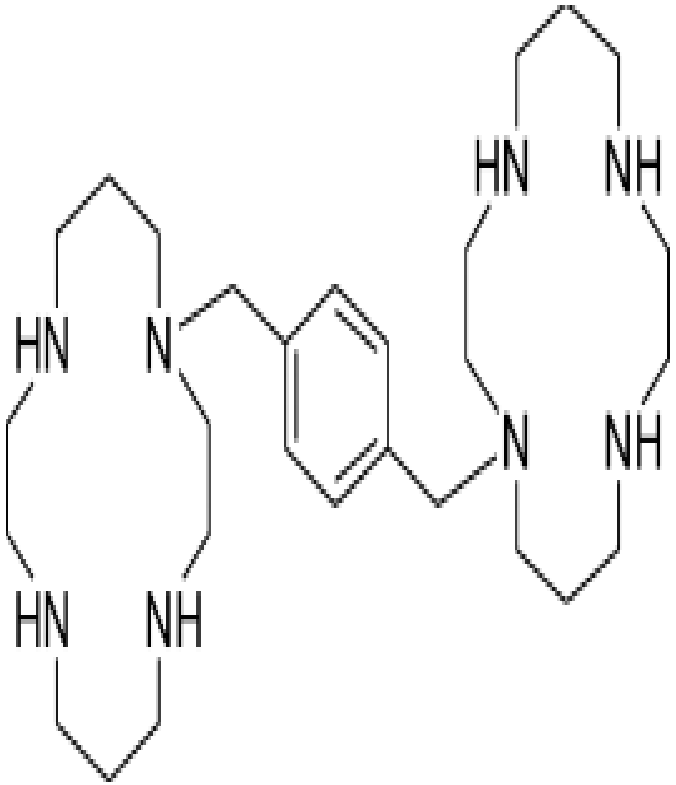
Medicinal inorganic chemistry

It is important to ask which parts ofthe active compound are essential for activity: the metal itself,the ligands, or the intact complex of metal plus, at least, some of the ligands?

Some metal compounds in clinical use

Compound Example (brand name)	Function	Comment
Active complexes		
cis-$[Pt^{II}Cl_2(NH_3)_2]$ (Cisplatin)	Anticancer	*trans*-isomer is inactive
$[Gd^{III}(DTPA)(H_2O)]^{2-}$ (Magnevist)	Extracellular contrast agent for MRI	Low toxicity
$[^{99m}Tc^{I}(CNCH_2C(CH_3)_2OCH_3)_6]^{+}$ (Cardiolite)	Myocardial imaging	Positively-charged complex taken up by the heart
Vitamin B_{12}	Coenzyme	Deficiency causes pernicious anaemia
Active metals		
Li_2CO_3	Prophylaxis for bipolar disorders	Li forms weak complexes, labile
$[Au^{I}$(thiomalate)] (Myocrisin)	Antirheumatoid arthritic	Facile thiol exchange on Au^{I}
Ammonium potassium Bi^{III} citrate (De-Nol)	Antibacterial, antiulcer	Strong binding of Bi to thiols, facile exchange
$Na_2[Fe^{II}(CN)_5(NO)]\cdot 2H_2O$ (Nipride)	Hypotensive	Releases NO, relaxes vascular muscles
(Bleomycin)	Anticancer	Requires Fe for DNA attack
p-xylyl-bicyclam-8HCl (AMD3100)	Anti-HIV, stem cell mobilization	May bind metals *in vivo*
$CaCO_3$, $Mg(OH)_2$	Antacid	Slow release of alkali
$La_2^{III}(CO_3)_3$ (Fosnol)	Chronic renal failure	Reduces phosphate absorption

Metallomacrocycles



- Cyclams:strong metal-chelating agents
- AMD3100 :used to treat cancer in the blood and immune in phase II
- Complexation of AMD3100 to Zn(II):enhances co-receptor binding strength and anti-HIV activity

Metallomacrocycles

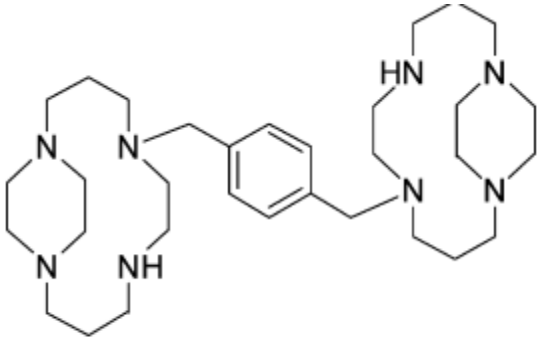


Chart 3. Constrained analogue of AMD3100.

- to rationalize the effects of cyclam configuration and to produce new specific antagonists for CXCR4

CXCR4:receptor number 4 for natural chemotactic cytokine proteins containing a conserved Cys-XCys disulfide sequence

Metallomacrocycles

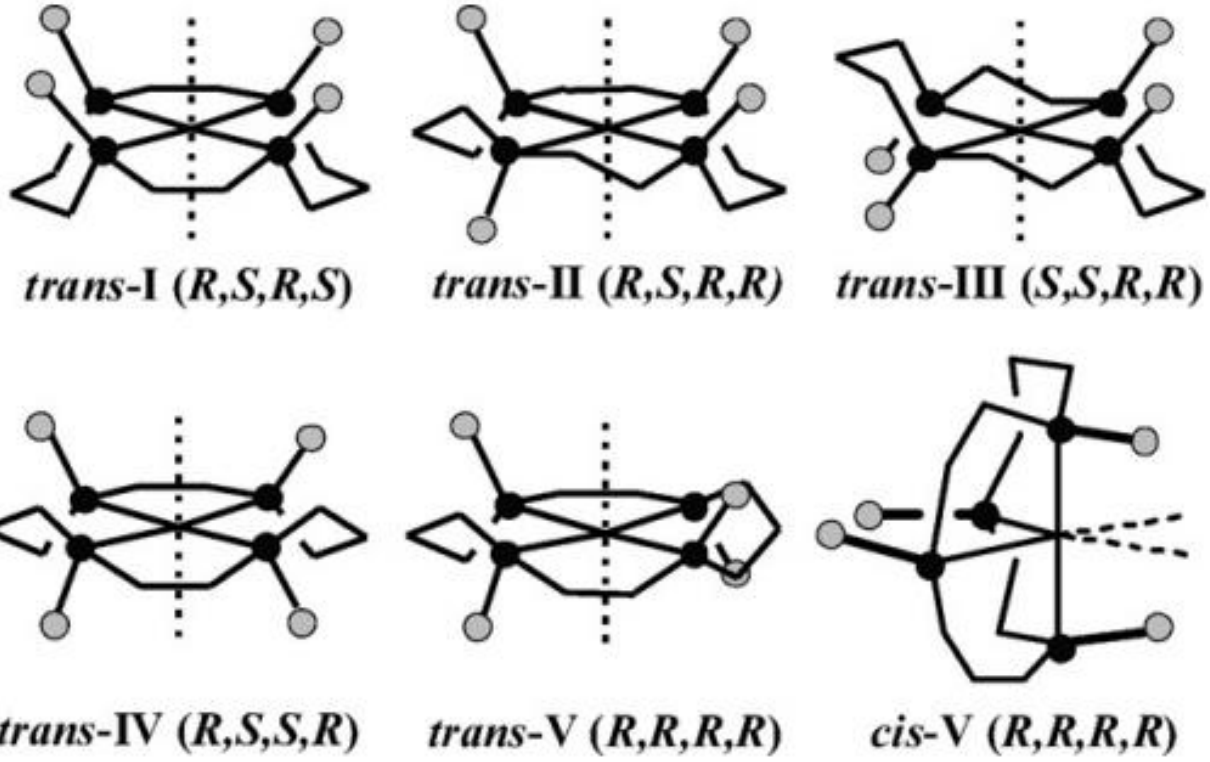
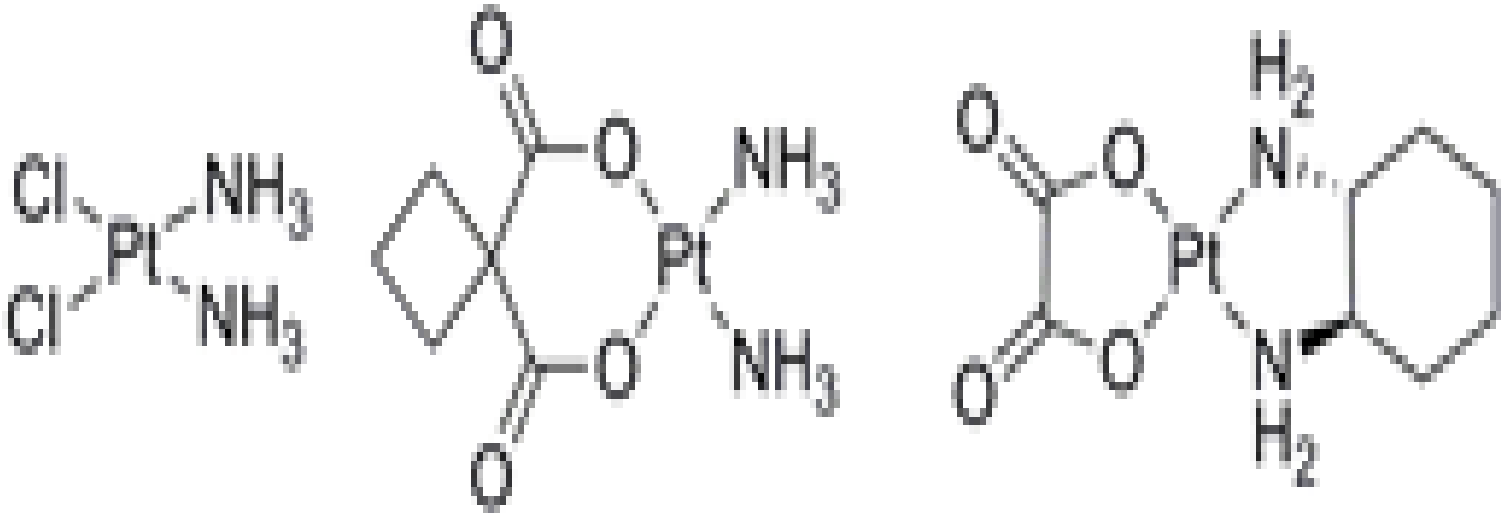


Chart 2. Structures of the major configurations of metal cyclam complexes. *Trans* configurations show the chiral N atoms with NH bonds pointing up or down, together with *cis*-V, the folded form of *trans*-V.

Photoactivated platinum complexes

- Cisplatin and Carboplatin
- exploring the platinum prodrugs which can be activated by light leading to the release of active antitumour agents



Cisplatin Carboplatin Oxliplatin

Photoactivated platinum complexes

- Photodynamic therapy:

I. selective damage of target tissue by using a photosensitizing drug and light

II. The photosensitizer absorbs energy from a light source and becomes excited to an energetically higher electronic state

Photoactivated platinum complexes

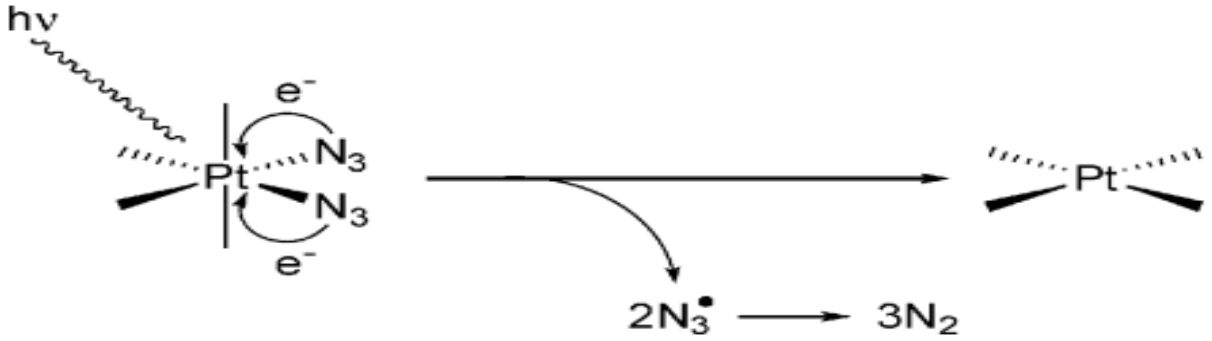


Chart 4. Possible mechanism for the photoreduction of a Pt(IV)-diazido complexes.

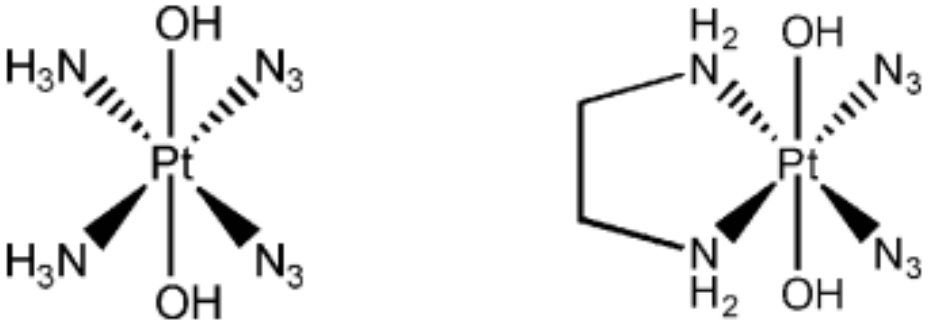
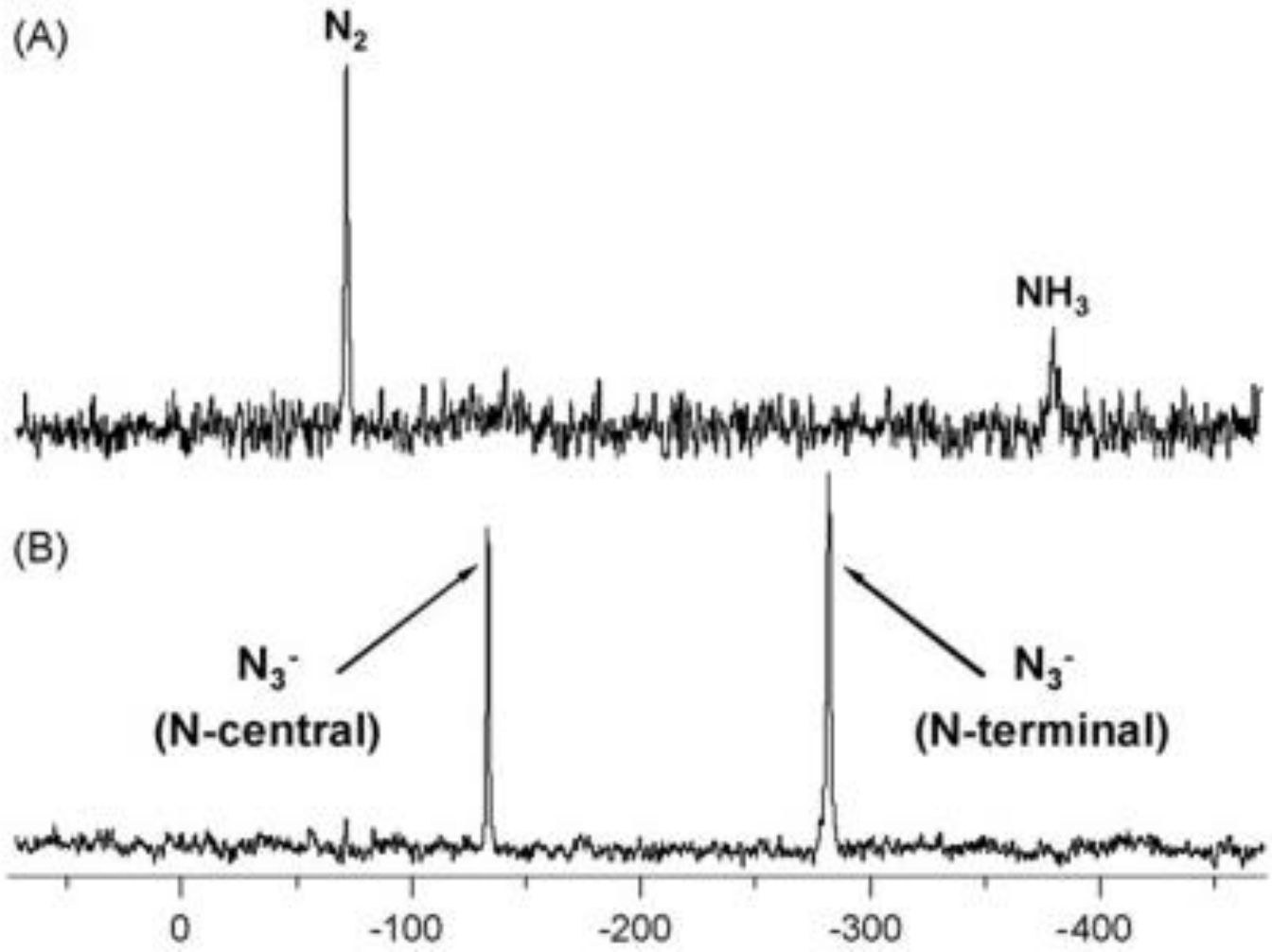


Chart 5. Chemical drawings of *cis,trans,cis*-$[Pt(N_3)_2(OH)_2(NH_3)_2]$ and *cis,trans*-$[Pt(N_3)_2(OH)_2(en)]$.

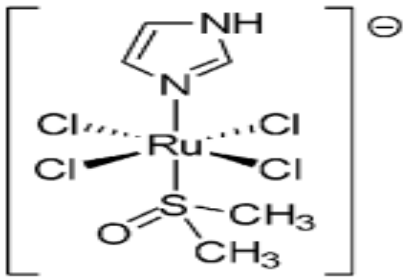
Photoactivated platinum complexes



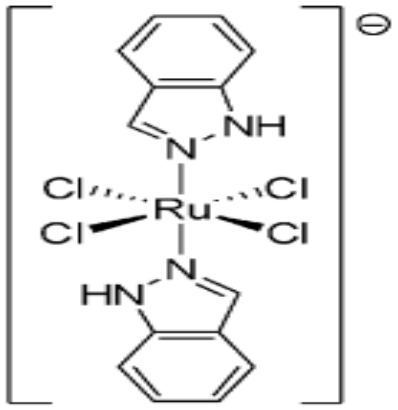
Metal arene complexes

- Titanocene dichloride:the cis-($TiCl_2$) motif would react with DNA in a similar manner to cisplatin

- Ru(III)ammines:[$RuCl_3(NH_3)_3$]



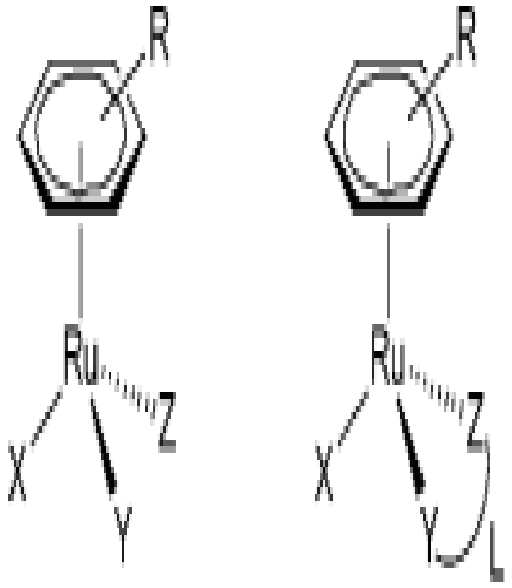
NAMI-A



KP1019

Chart 6. Ruthenium anticancer complexes *trans*-[$RuCl_4$(Im)(DMSO)]ImH (NAMI-A) and *trans*-[$RuCl_4(Ind)_2$]IndH (KP1019).

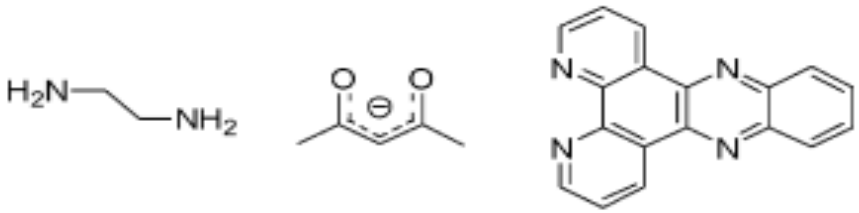
Metal arene complexes



- A typical structure of a half-sandwich “piano-stool” [η^6-arene)Ru(X)(Y)(Z)] complex
- the arene forms the seat of the piano-stool
- the ligands resemble the legs. Linking the ligands Y and Z to form a bidentate chelating ligand (L) seems to be advantageous for anticancer activity

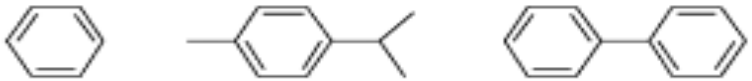
Metal arene complexes

Examples of L:



en acac dppz

Examples of arenes:



benzene *p*-cymene biphenyl

dihydroanthracene tetrahydroanthracene

Chart 7. Typical structures of Ru(II) half-sandwich complexes and selected examples of chelating ligands (L) and arenes (Ph-R).

Organometallic Half-Sandwich Iridium Anticancer Complexes

- Contents:

I. Synthesis a serous of low-spin $5d^6$Ir III organometallic half-sandwich complexes [(η5-Cp^x)Ir(XY)Cl]$^{0/+}$

II. Hydrophobicity(logP), cell and nucleus accumulation of Ir correlate with cytotoxicity

III. The ability to displace DNA intercalator ethidium bromide

IV. The hydrophobicity and intercalative ability of Cp^{xph} and Cp^{xbiph}

Introduction

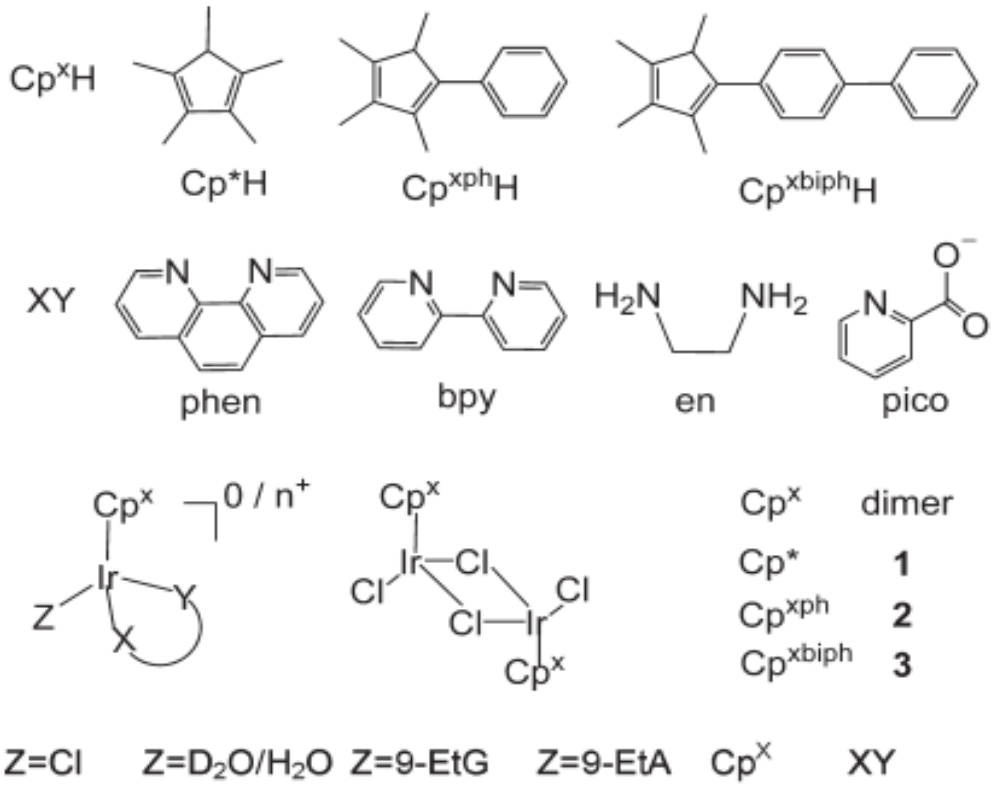
I. A few studies of organometallic IrIII complexes have been reported

II. The arene is important in determining the anticancer activity and nature of the DNA distortions

III. Neutral arene ligands do not stabilize IrIII ,In contrast,

negatively charged pentamethylcyclopentadienyl (Cp*) is an excellent stabilizing ligand for IrIII ,tetramethyl(phen-yl)cyclopentadienyl (Cp^{xph}) and tetramethyl (biphenyl)cyclopentadienyl (Cp^{xbiph})have been used as ligands in iridium complexes.

Chart 1. Iridium Cyclopentadienyl Complexes Studied in This Work



4	4A	4G		Cp*	phen
5	5A	5G		Cp^{xph}	phen
6	6A	6G		Cp^{xbiph}	phen
7	7A	7G		Cp*	bpy
8	8A	8G		Cp^{xph}	bpy
9	9A	9G		Cp^{xbiph}	bpy
10	10A	10G		Cp*	en
11		11G		Cp^{xph}	en
12	12A	12G	12Ad	Cp*	pico
13	13A	13G	13Ad	Cp^{xph}	pico
14	14A	14G	14Ad	Cp^{xbiph}	pico

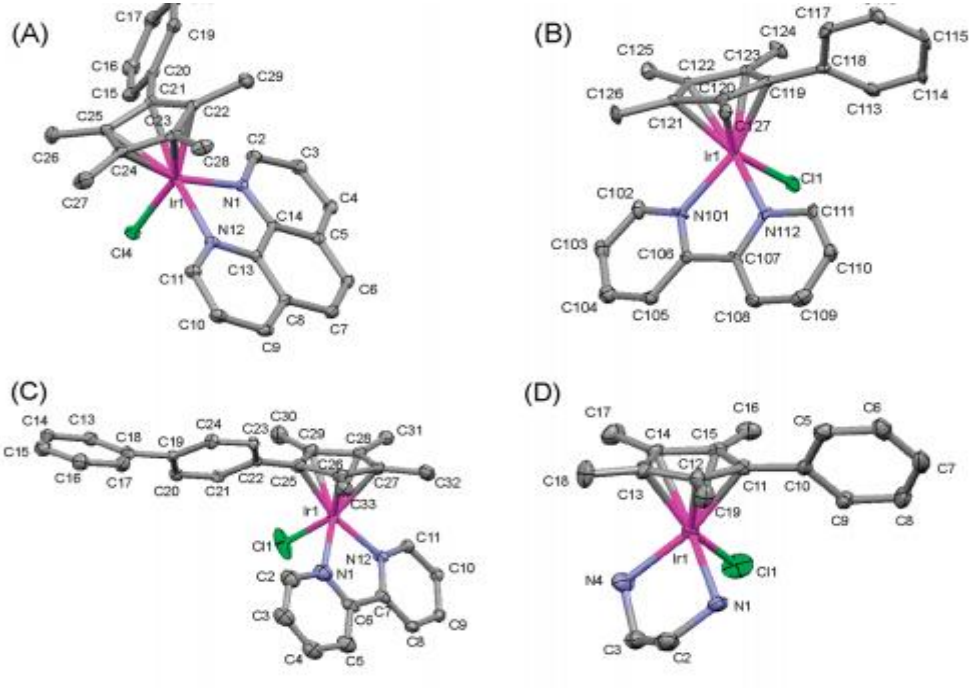
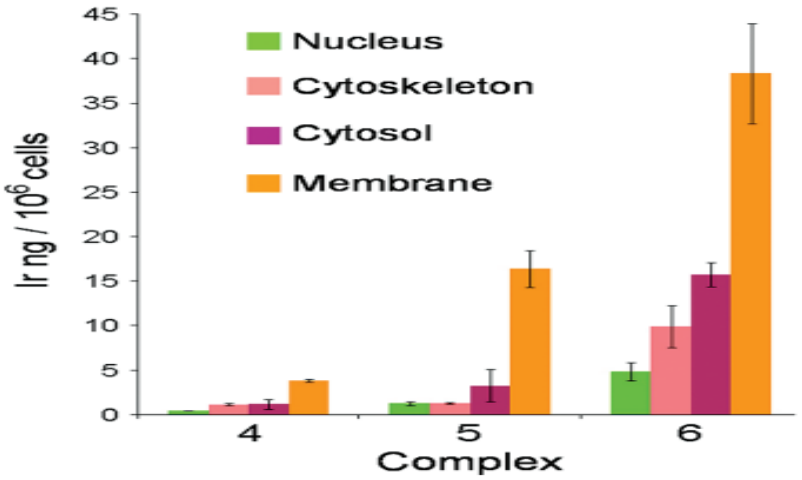

(A)
C17
C19
C16
C20
C29
C15
C21
C22
C25
C23
C26
C28
C2
C3
C24
C27
Ir1
N1
C4
C14
N12
C5
Cl4
C13
C11
C6
C10
C8
C7
C9
(B)
C117
C124
C115
C125
C122
C123
C118
C126
C120
C119
C114
C113
C121
C127
Ir1
Cl1
C102
N101
C111
N112
C103
C106
C107
C110
C104
C105
C108
C109
(C)
C14
C13
C24
C30
C15
C18
C19
C23
C29
C28
C31
C26
C16
C17
C20
C21
C22
C25
C27
C32
C33
Ir1
Cl1
C11
N12
C10
C2
N1
C3
C7
C9
C6
C8
C4
C5
(D)
C17
C16
C5
C6
C14
C15
C12
C7
C18
C13
C11
C10
C19
C9
C8
Ir1
Cl1
N4
N1
C3
C2

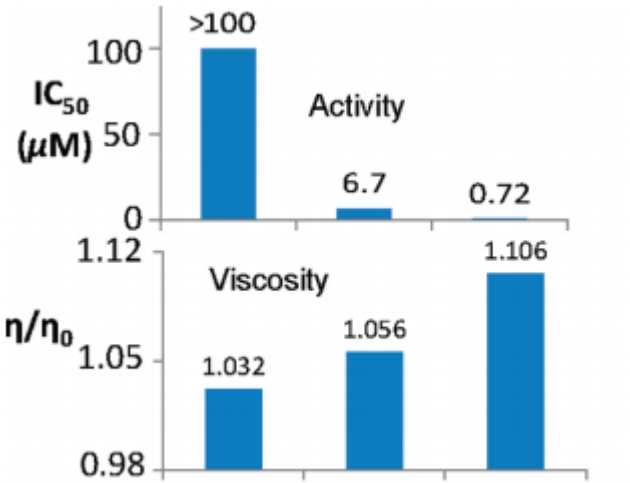
Table 6. Iridium Accumulation and Binding to DNA in A2780 Human Ovarian Cancer Cells[a]

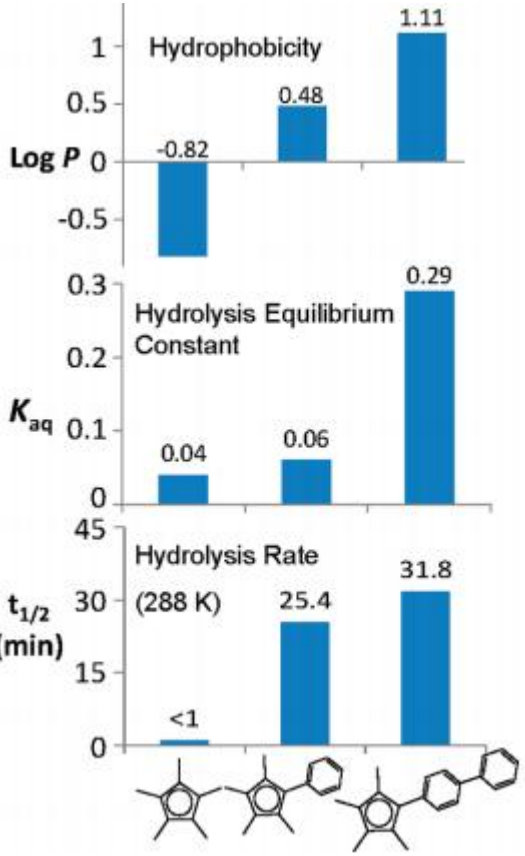
	cell accumulation (ng Ir/10^6 cells)		DNA binding (ng Ir/10^6 cells)	
complex	mean	SD	mean	SD
4	3.9	0.2	0.3	0.04
5	23.5	3.7	1.3	0.3
6	88.8	20.0	5.3	1.6



- Cell Accumulation and DNA Binding
- Distribution of Iridium in Cell Fractions.

Cytotoxicity toward human cancer cells





Diazido Mixed-Amine Platinum(IV) Anticancer Complexes Activatable byVisible-Light Form Novel DNA Adducts

- Content:

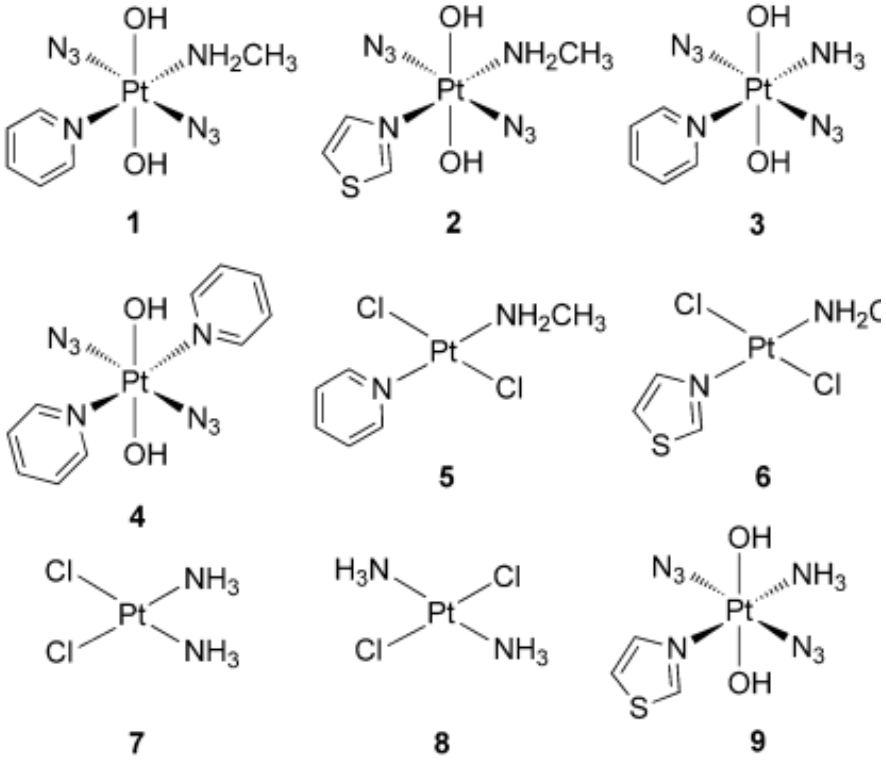
I. The synthesis, X-ray crystallographic and spectroscopi-c properties of photoactivatable diazido complexes Z,Z,Z-[$Pt(N3)_2(OH)_2(MA)(Py)$](1) and Z,Z,Z-[$Pt(N3)_2(-OH)_2(MA)$-(Tz)] (2)

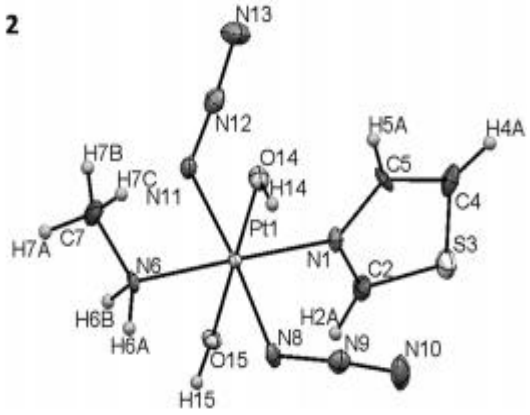
II. Interpret complexes 1 and 2 photophysical properties

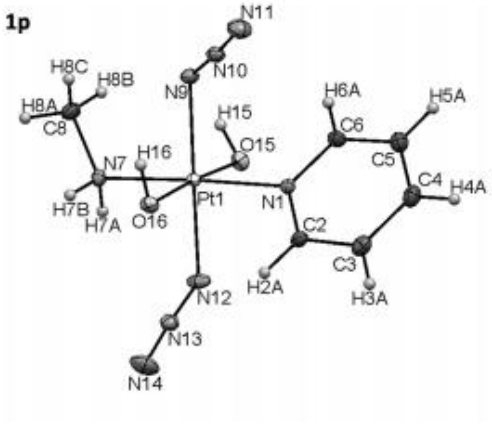
III. Photoactivated1and 2 form both mono- and bifunctional DNA lesions, with preference for G and C

IV. Complexes1 and 2 can therefore give rapid potent photo-cytotoxicity and novel DNA lesions in cancer cells, with no activity in the absence of irradiation

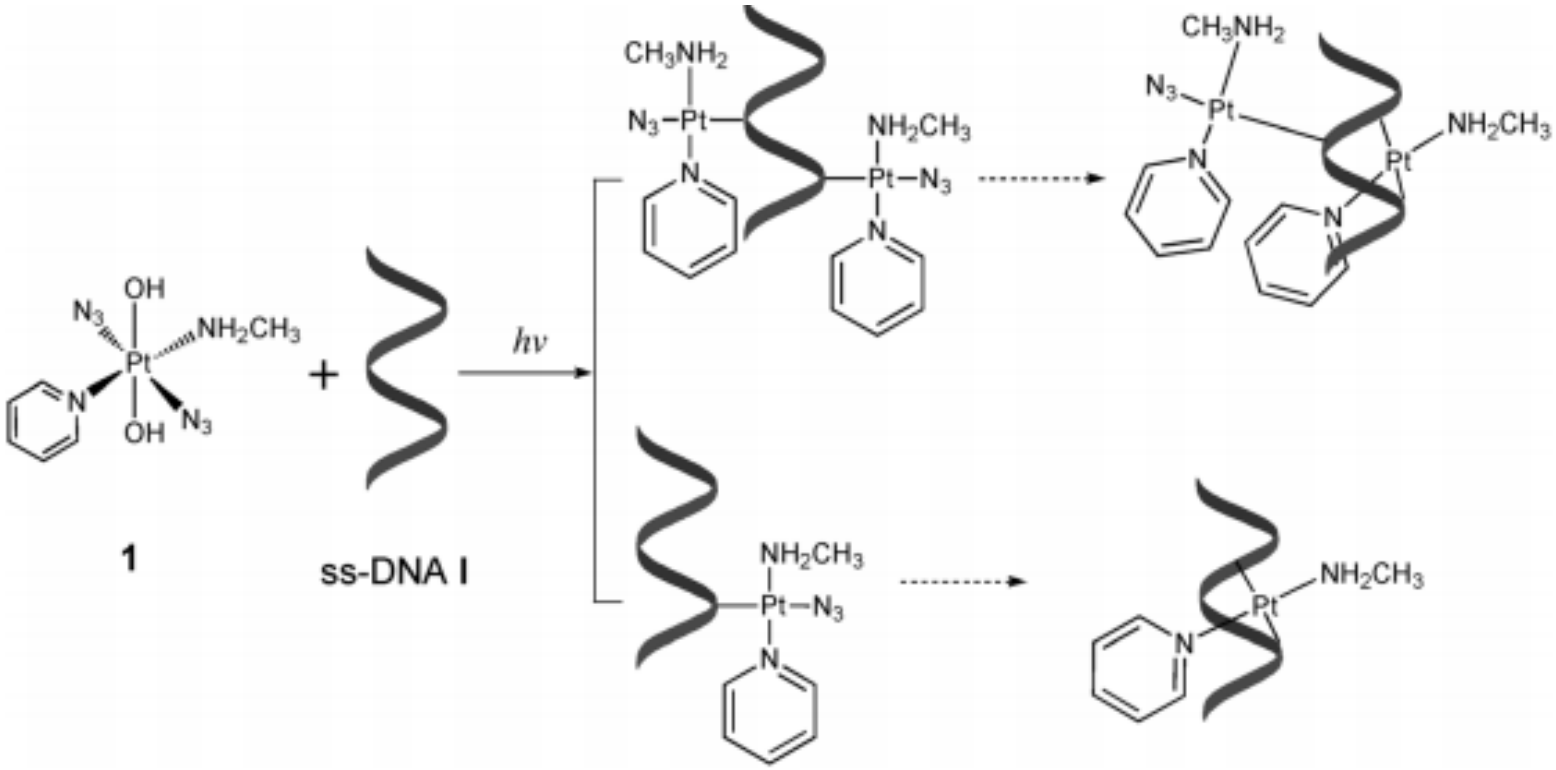
Structures of complexes and its X-ray crystal structure







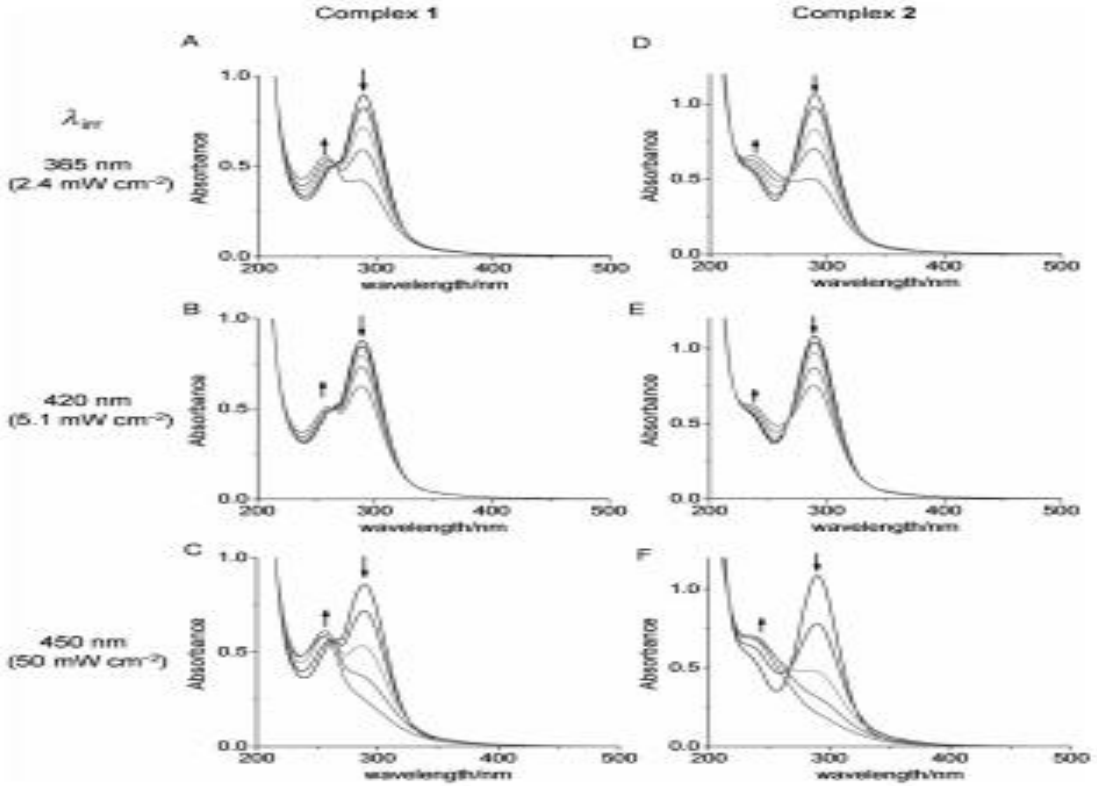
Photoinduced reaction of complex1with ss-DNA 1

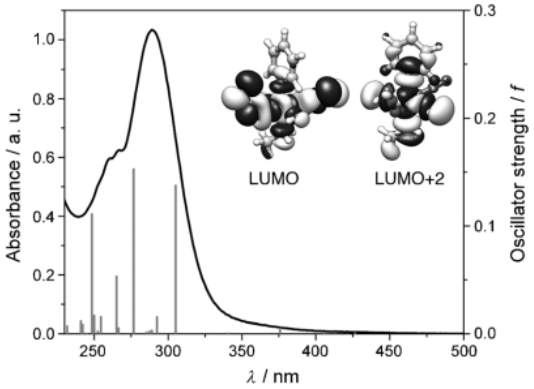


Spectroscopic properties of compleses

- In the absence of light, complexes 1 and 2 were not substantially cytotoxic
- Upon irradiation with UVA (5 J cm^{-2}; λmax=365 nm), the cytotoxicities of complexes1, 2 and 9 dramatically increased and were significantly greater than that of cisplatin (50–65-fold) under the experimental conditions used
- Visible blue light also caused cell death in the presence of the complexes

Spectroscopic properties of compleses





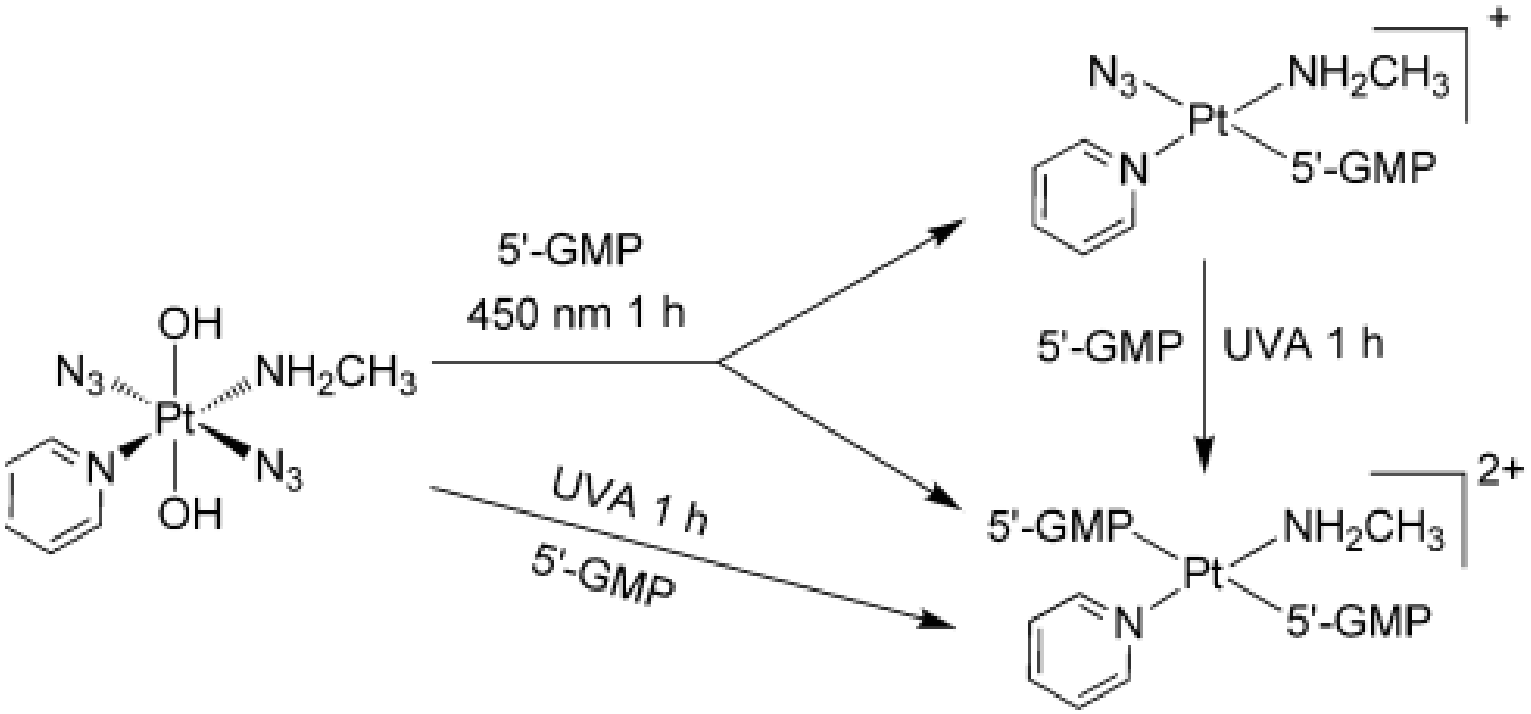
Photocytotoxicity

Table 2. Phototoxicity of Pt^{IV} complexes **1**, **2**, and **9**, in comparison with complexes **3**, **4** and cisplatin (**7**).

	IC_{50}[a] [μM]											
	HaCaT			A2780			A2780cis			OE19		
	UVA	TL03[b]	sham[c]	UVA	TL03	sham	UVA	TL03	sham	UVA	TL03	sham
1	2.6 (1.8–3.8)	14.7 (10.8–19.9)	>236.3[d]	2.3 (2.0–2.7)	6.6 (4.2–10.5)	>236.3	4.4 (2.8–6.8)	13.2 (11.6–15.1)	>236.3	10.1 (8.3–12.4)	13.9 (6.0–32.2)	>236.3
2	3.5 (2.7–4.5)	11.2 (8.5–14.8)	>232.9	3.2 (3.0–3.5)	28.2 (11.4–69.9)	>232.9	5.3 (3.2–8.5)	6.4 (1.6–24.9)	>232.9	6.2 (5.5–6.9)	19.3 (15.4–24.2)	>232.9
3[5]	6.8 (5.4–8.6)	85.9 (43.9–168.6)	>244.4	3.1 (2.9–3.3)	NT[e]	>244.4	16.9 (14.2–20.3)	NT[e]	>244.4	10.0 (8.3–12.1)	32.0 (13.6–75.2)	>244.4
4[6]	2.3 (0.8–6.5)	6.8 (5.2–8.9)	>212.3	1.1 (0.6–1.9)	8.3 (3.4–20.4)	>212.3	14.5 (2.1–21.2)	NT[e]	>212.3	4.7 (4.0–5.4)	8.4 (6.5–10.8)	>212.3
7	143.7 (124–166)	NT[e]	173.1 (153–195)	151.3 (133–172)	NT[e]	152.0 (137–168)	261.0 (214–319)	NT[e]	229.0 (191–273)	NT[e]	NT[e]	NT[e]
9	4.5 (2.9–7.0)	19.8 (18.2–21.5)	>241.0	5.5 (4.6–6.5)	NT[e]	186.9 (170–205)	9.9 (8.7–11.2)	NT[e]	>241.0	NT[e]	NT[e]	NT[e]

[a] The concentration of complex that inhibited dye uptake by 50%. The lower value indicates the higher toxicity to cells. Each value is the mean of two or three independent experiments performed in triplicate. The figures in brackets are the 95% confidence intervals for the IC_{50} values. [b] TL03 is a blue fluorescence source (λ_{max} = 420 nm). [c] Sham irradiated samples. [d] Greater than sign indicates an IC_{50} value greater than the concentration range used. [e] Not tested.

Photoreactions with 5’-guanosine monophosphate



Scheme 3. Photoreaction pathways of complex **1** with 5′-GMP upon irradiation with UVA or 450 nm light.

Photoreactions with 5’-guanosine monophosphate

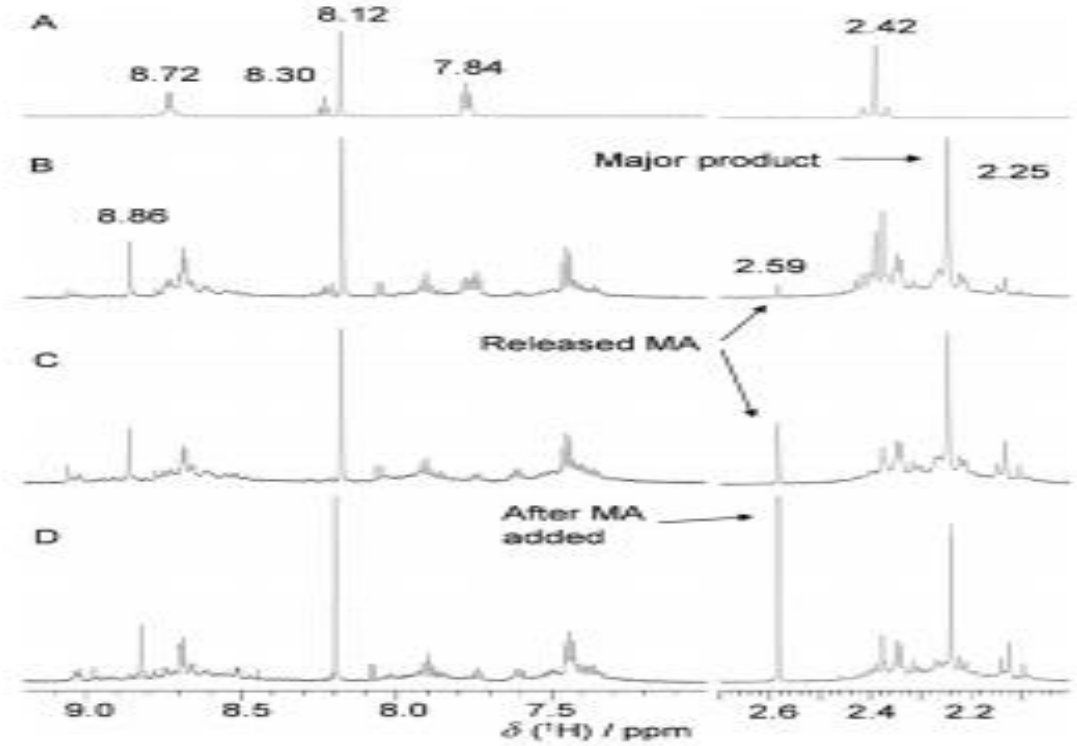


Figure 4. ^{1}H NMR spectra for reaction of complex **1** (3.9 mM) with 5’-GMP (7.8 mM) in D_2O (initial pH adjusted to 7.4) upon irradiation at 450 nm (50 mW cm^{-2}, 298 K) for: A) 0 h (dark), B) 1 h (180 J cm^{-2}), and C) 3 h (540 J cm^{-2}); D) after irradiation the NMR sample was spiked with 1 mol equiv of free MA.

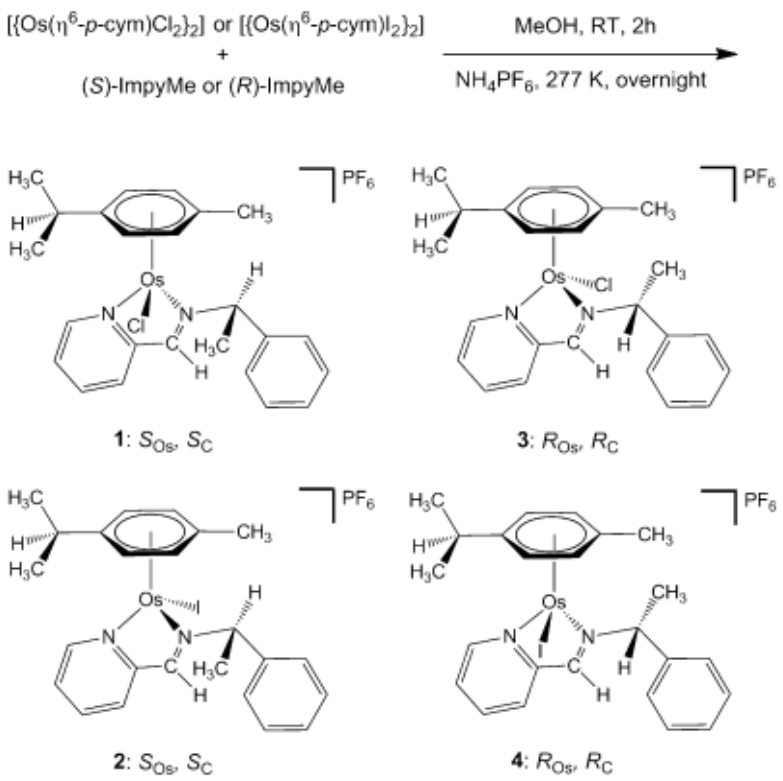
Mirror-Image Organometallic Osmium Arene Iminopyridine Halido Complexes Exhibit Similar Potent Anticancer Activity

- Contents:

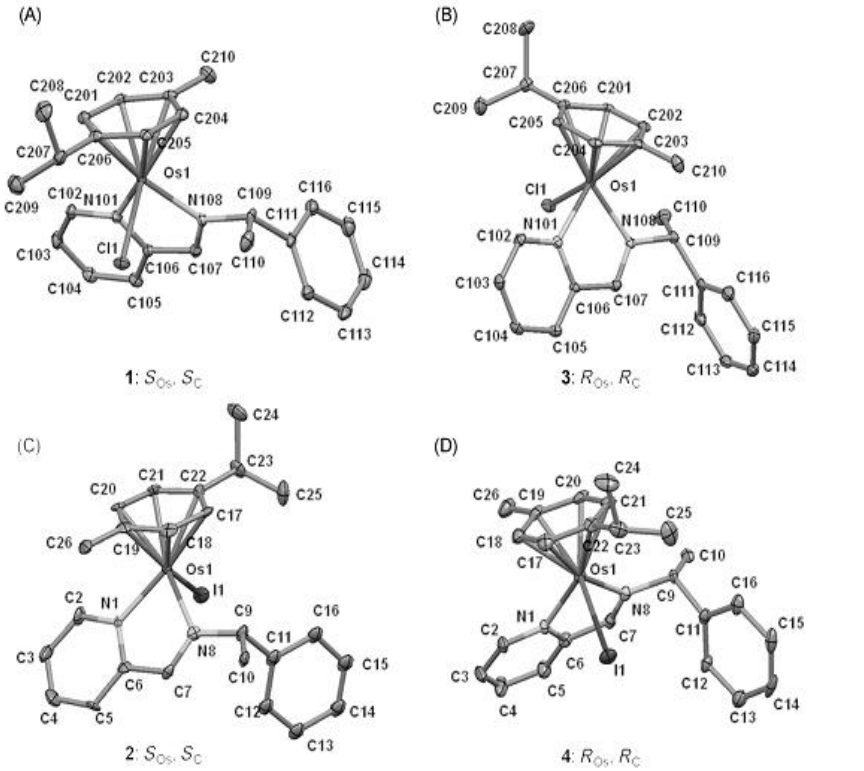
I. Four chiral OsII arene anticancer complexes have been isolated by fractional crystallization and showed different anticancer activity.

II. the synthesis of the anticancer OsII arene iminopyridine (Impy) complex, [Os(η^6 -p-cym)(Impy-OH)I]PF6

Synthesis characterization and crystal structures

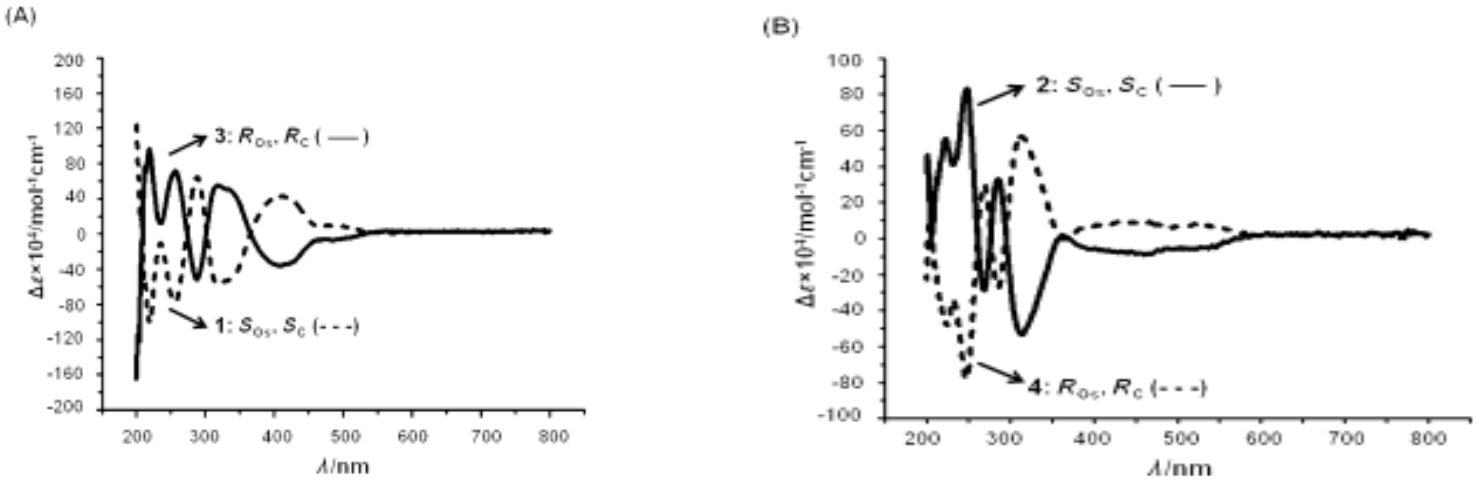


Scheme 1. Synthetic route for the chiral Os^{II} complexes used in this work.



gure 1. X-ray crystal structures of **1** (A), **2** (C), **3** (B), and **4** (D). Thermal ellipsoids are shown at 50% prob-
ility. The hydrogen atoms and counterion have been omitted for clarity.

Circular dichroism



- Circular dichroism spectra for the two pairs of OsII arene iminopyridine complexes: (A)1 and 3; (B) 2 and 4.
- Confirm that the two molecular structures within the two pairs of OsII iminopyridine complexes are mirror images

Anticancer activity

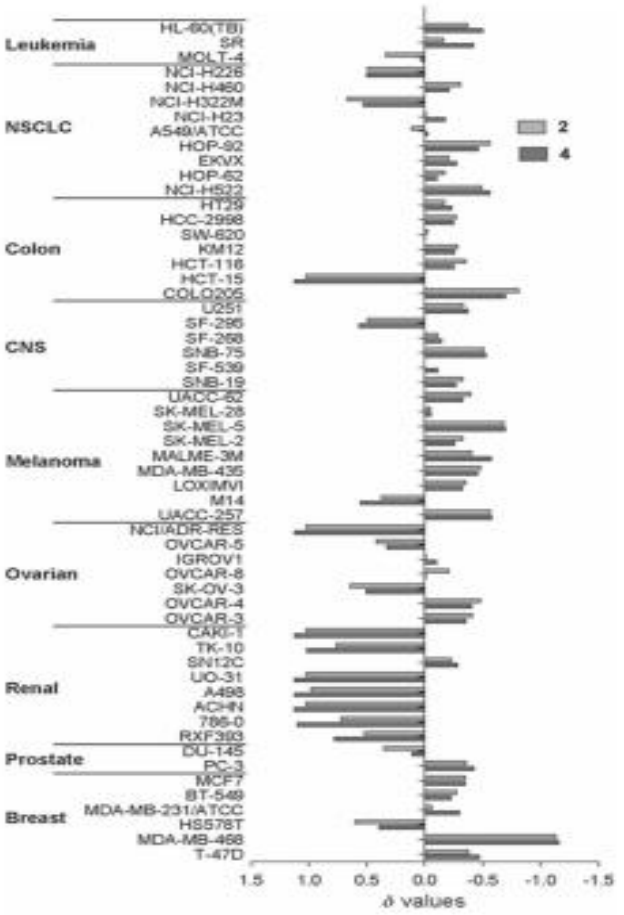
Table 5. Mean IC_{50}, TGI and LC_{50} values from the NCI-60 data for complexes **2** and **4**.

Complex[a]	IC_{50} [μM][b]	TGI [μM][c]	LC_{50} [μM][d]
(S_{Os},S_C)-[Os(η^6-*p*-cym)(ImpyMe)I]PF_6 (**2**)	9.55	61.7	91.2
(R_{Os},R_C)-[Os(η^6-*p*-cym)(ImpyMe)I]PF_6 (**4**)	7.58	53.7	89.1
cisplatin[e]	1.49	9.33	44.0

Table 4. IC_{50} values for the A2780 ovarian cancer cell line.

Complex	IC_{50} [μM]
(S_{Os},S_C)-[Os(η^6-*p*-cym)(ImpyMe)Cl]PF_6 (**1**)	22.3 (±1.6)
(S_{Os},S_C)-[Os(η^6-*p*-cym)(ImpyMe)I]PF_6 (**2**)	1.9 (±0.2)
(R_{Os},R_C)-[Os(η^6-*p*-cym)(ImpyMe)Cl]PF_6 (**3**)	18.3 (±1.7)
(R_{Os},R_C)-[Os(η^6-*p*-cym)(ImpyMe)I]PF_6 (**4**)	0.60 (±0.02)
(R_{Os},R_C) and (S_{Os},R_C)-[Os(η^6-*p*-cym)(ImpyMe)Cl]PF_6 mixture[a]	19.0 (±1.1)
cisplatin	2.0 (±0.2)

[a] Ratio approximately 1:1.



Thank you