Silver(I) Metallotherapeutics derived from the chemical modification of anti-inflammatory or anti-biotic drugs

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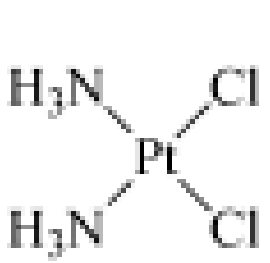
Silver(I) metal drugs

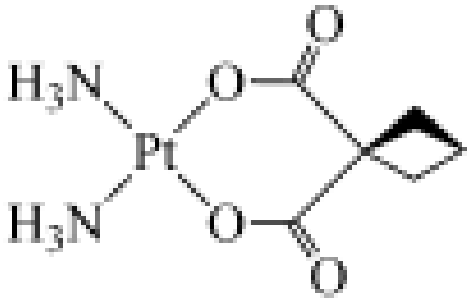
The biomedical applications of Ag(I) compounds are related mostly to their antibacterial action, which appears to involve interaction with DNA.

A similar interaction of the metal with DNA may also be the cause of the antitumor action of certain Ag(I) metal drugs.

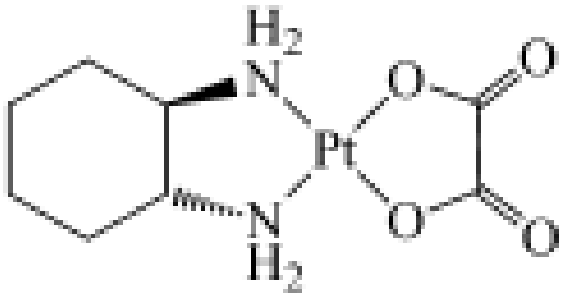
Cisplatin and carboplatin have a wide range of applications in cancer chemotherapy. **Since the discovery of the anti-proliferative properties of cisplatin, many platinum compounds have been synthesized, characterized and screened as anticancer agents**.



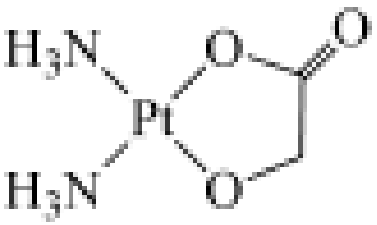
cisplatin



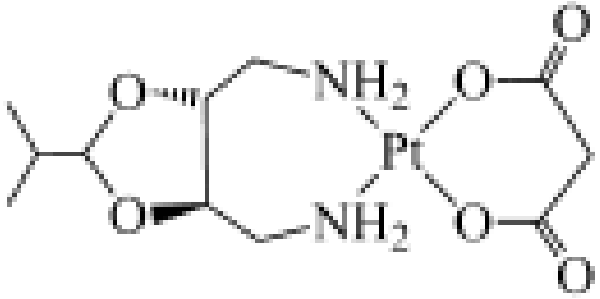
carboplatin



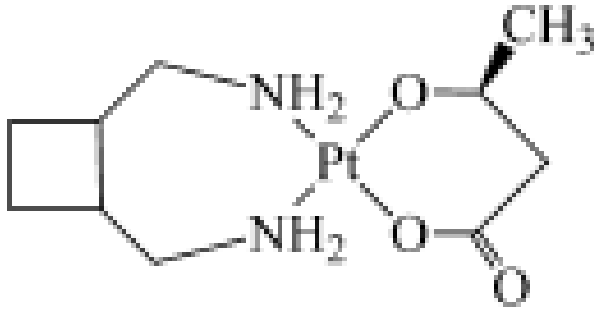
oxaliplatin



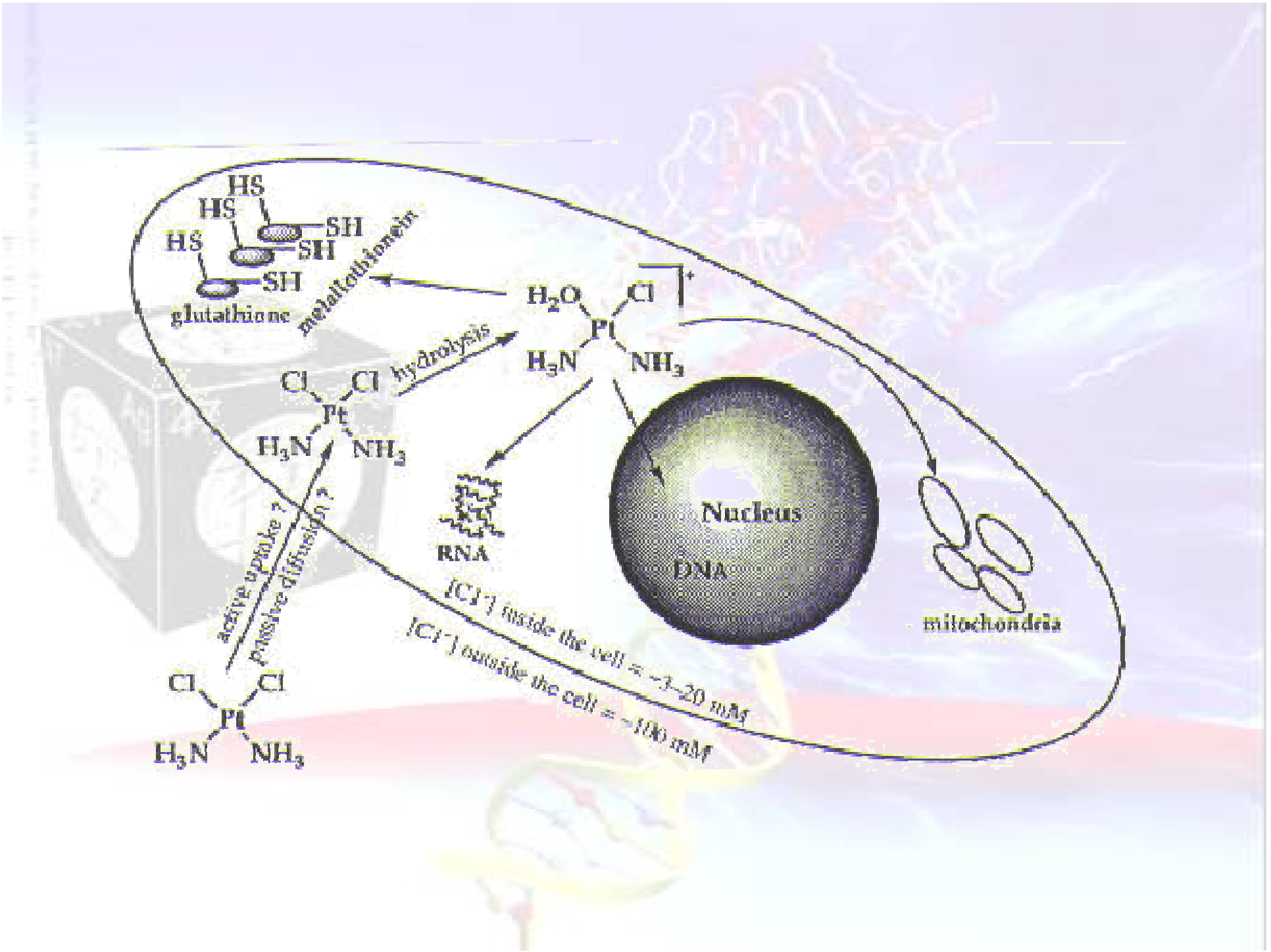
nedaplatin



heptaplatin

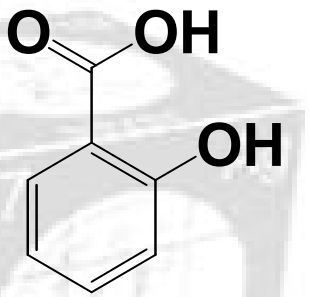


lobaplatin

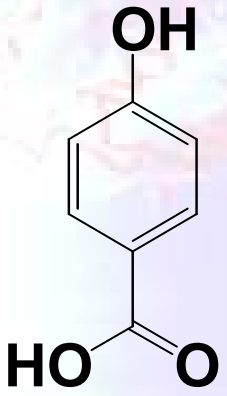

HS
HS
SH
HS
SH
SH
glutathione
metallothionein
H_2O
Cl
Pt
H_3N
NH_3
hydrolysis
Cl
Cl
Pt
H_3N
NH_3
RNA
Nucleus
DNA
mitochondria
active uptake ?
passive diffusion ?
[Cl⁻] inside the cell ≈ ~3–20 mM
[Cl⁻] outside the cell ≈ ~100 mM
Cl
Cl
Pt
H_3N
NH_3

NSAIDs

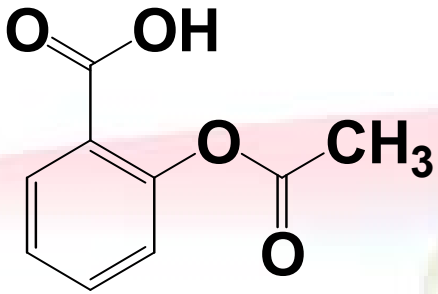
Several epidemiological, clinical and experimental studies have shown that Nonsteroidal Anti-inflammatory Drugs (NSAIDs) such as salicylic acid, aspirin, naproxen etc are promising cancer chemopreventive agents.



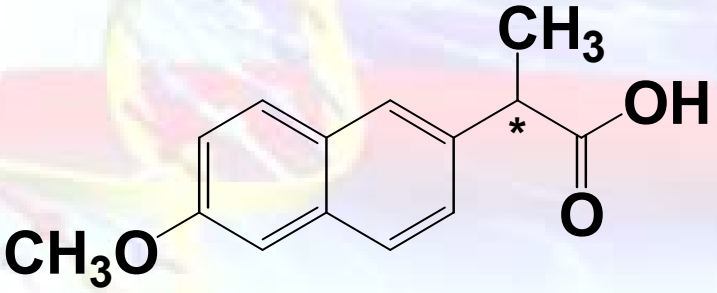
$salH_2$



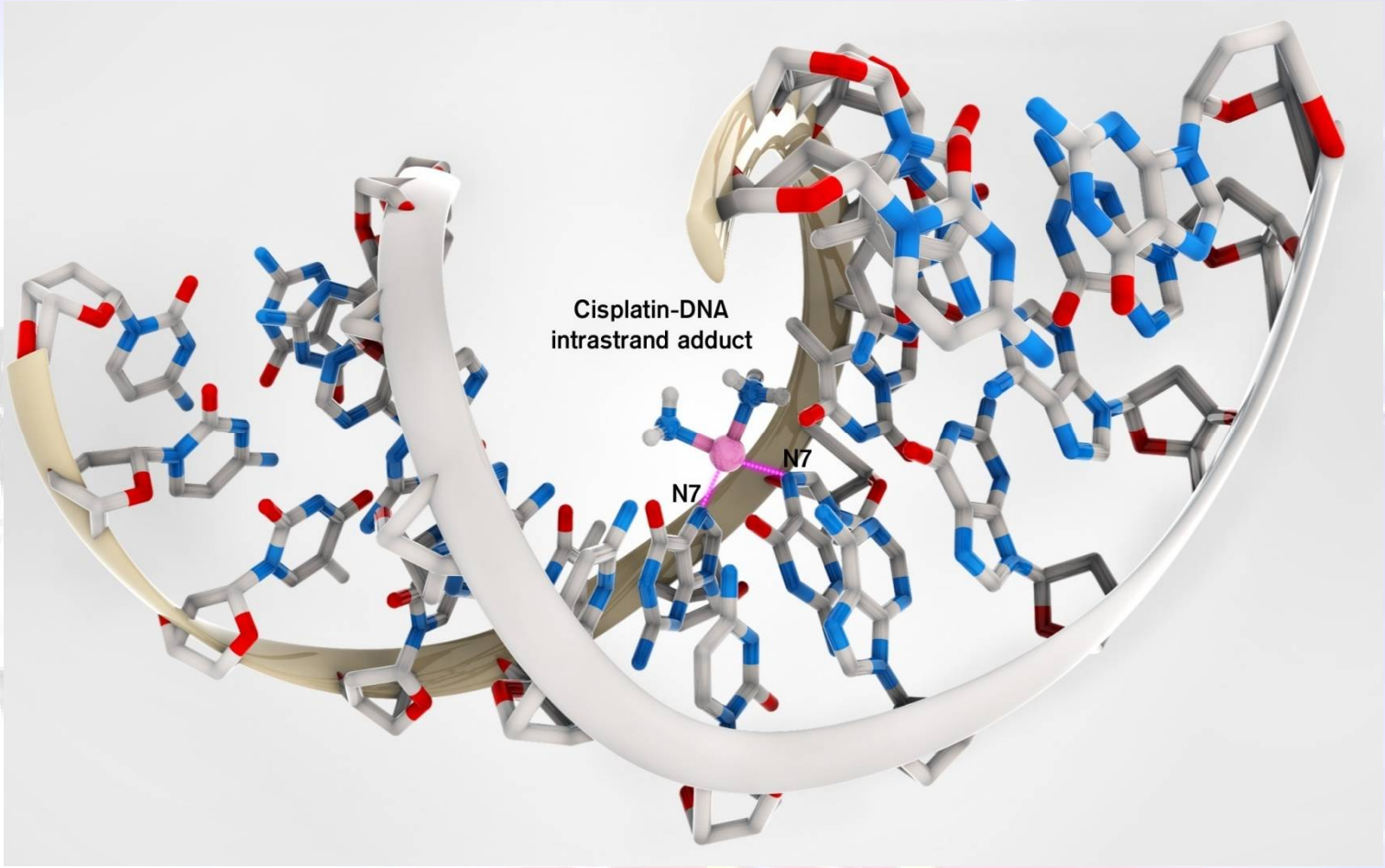
$p\text{-}HbzaH_2$



aspH



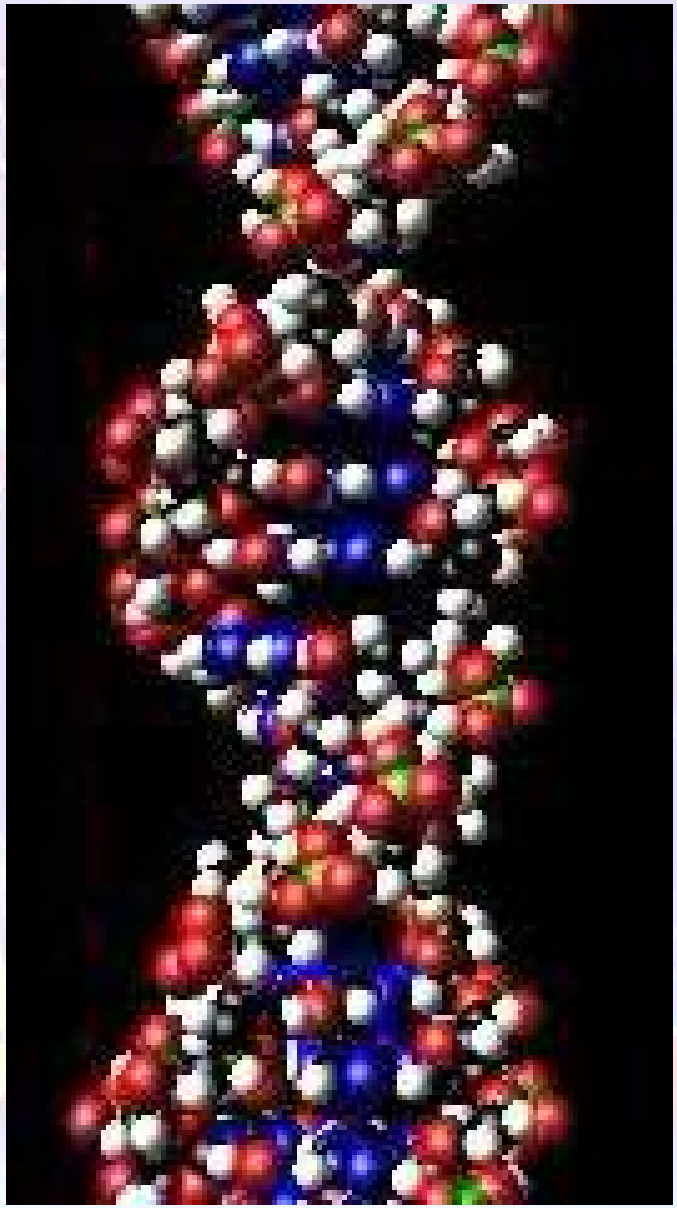
naproxen



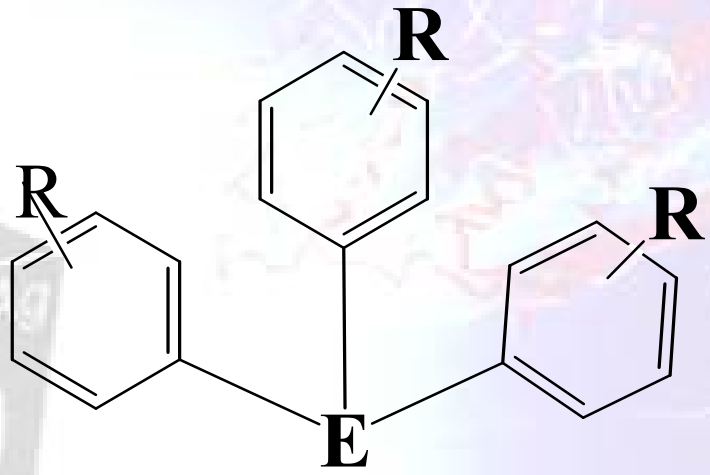
DNA is targeted by current chemotherapeutics of cancers.

Most of NSAIDs are anionic at physiological pH preventing their approach to the poly anionic DNA backbone.

The combination of a NSAID with a metal ion such as silver(I) is expected to allow the approach of the compound to DNA.

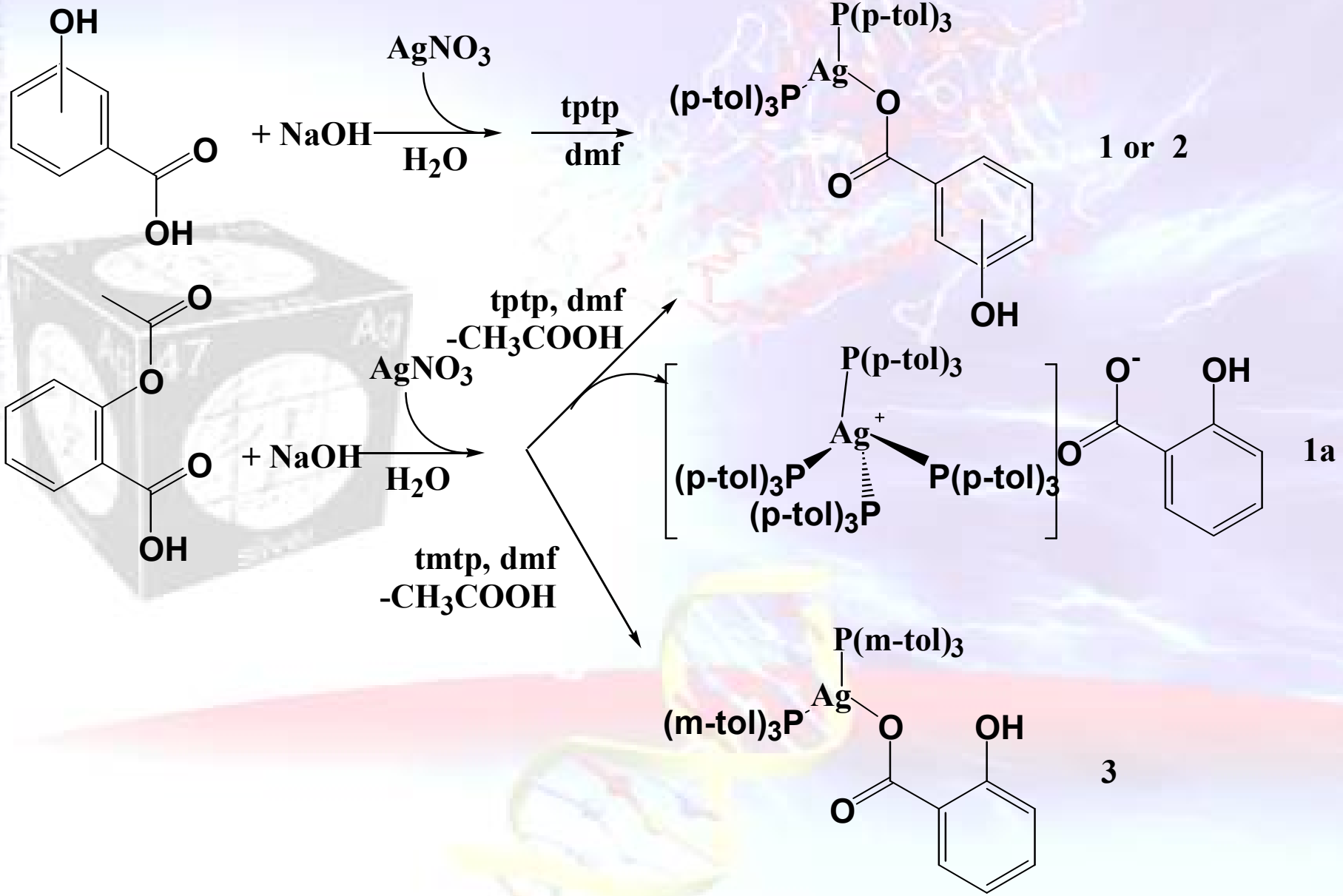


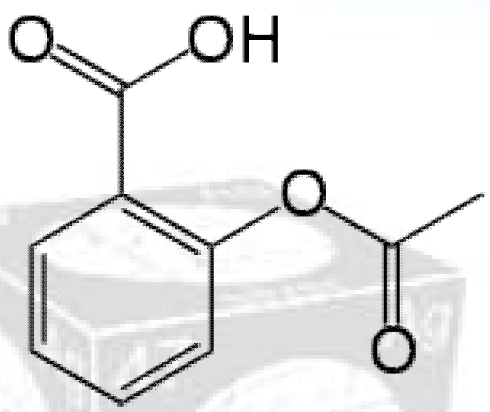
The lipophilicity of the compounds can be adjusted with the Mitochondriotropic triaryl-phosphines, arsines or stibines (Ar_3E E= P, As, Sb)



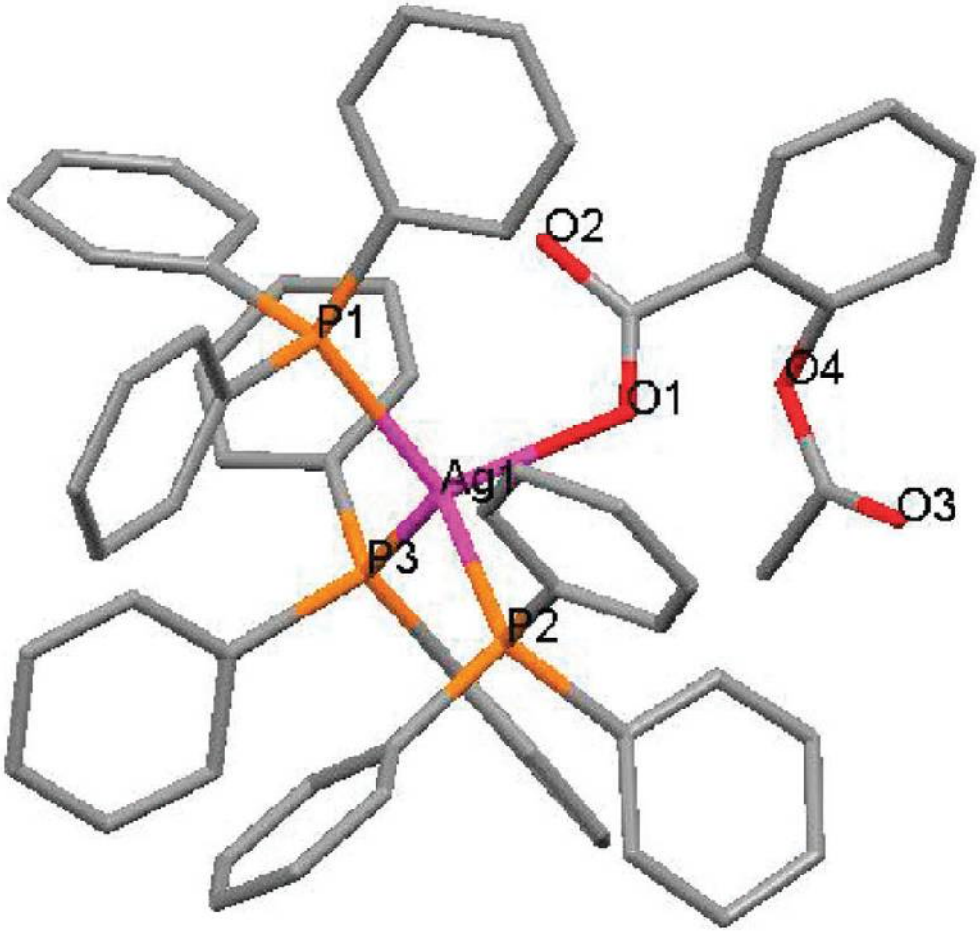
E= P and R= H (tpp)
E=P and R= p-Me- (tptp)
E=P and R= m-Me- (tmtp)
E=P and R= o-Me- (totp)
E= As and R= H (tpAs)
E= Sb and R= H (tpSb)

Synthesis of $[Ag(tptp)_2(salH)]$, $[Ag(tptp)_2(p\text{-}Hbza)]$ and $[Ag(tmtp)_2(salH)]$, $\{[Ag(tpp)_3(napr)](H_2O)\}$ and $[Ag(tptp)_2(napr)]$





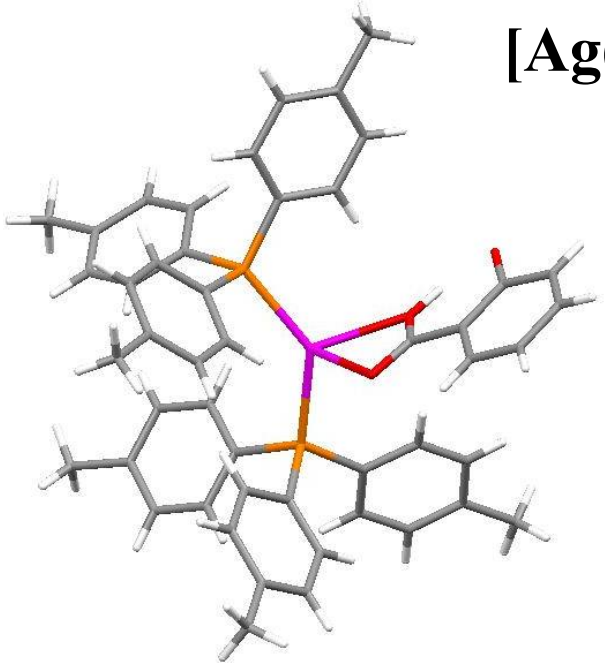
Aspirin (aspH)

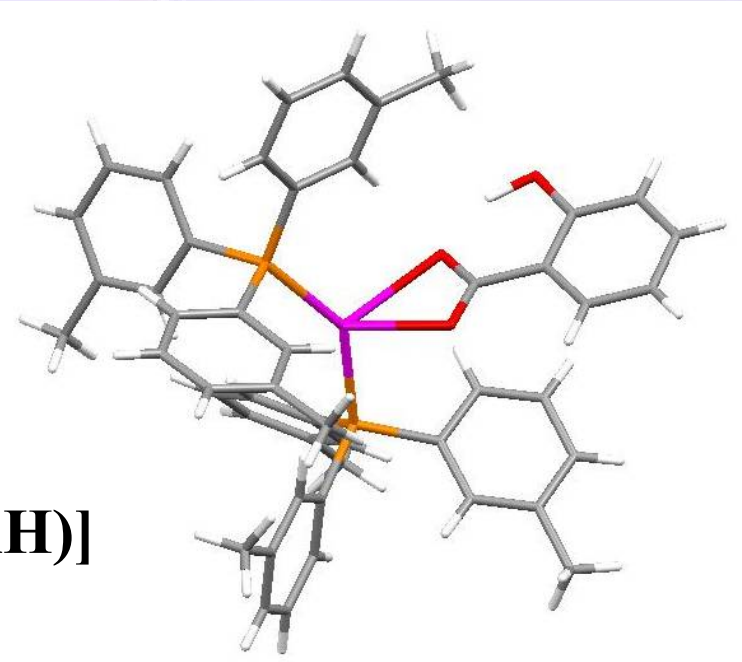


{[Ag(tpp)$_3$(asp)](dmf)}

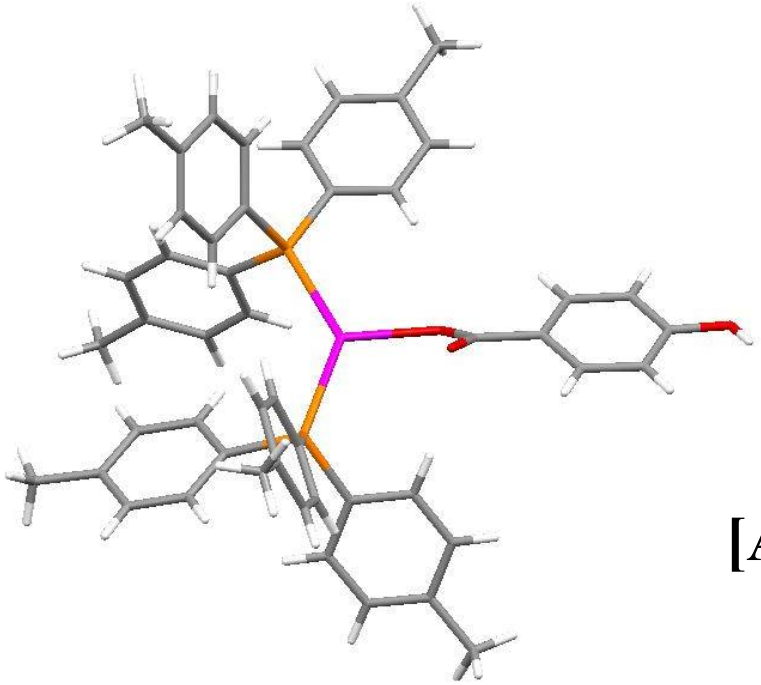
Ag1–P1 = 2.515(2), Ag1–P2 = 2.554(3), Ag1–P3 = 2.528(3), Ag1–O1 = 2.395(10), O1–C55 = 1.144(18), O2–C55 = 1.287(17), O3–C62 = 1.16(2), O4–C61 = 1.388(17), O4–C62 = 1.303(18), P1–Ag1–P2 = 109.32(9), P1–Ag1–P3 = 115.37(8), P1–Ag1–O1 =110.4(2), P2–Ag1–P3= 117.09(8), P2–Ag1–O1 = 101.4(2),P3–Ag1–O1 = 101.9(3).

$[Ag(tptp)_2(salH)]$

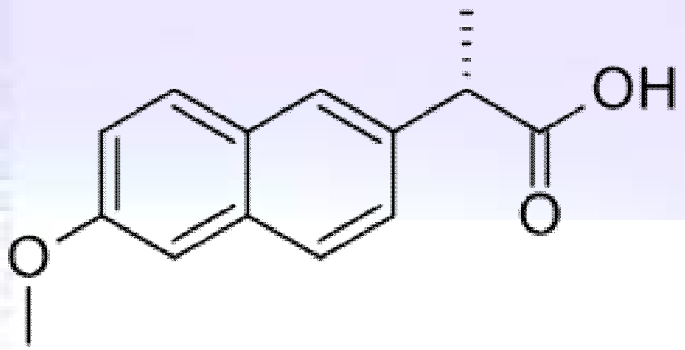




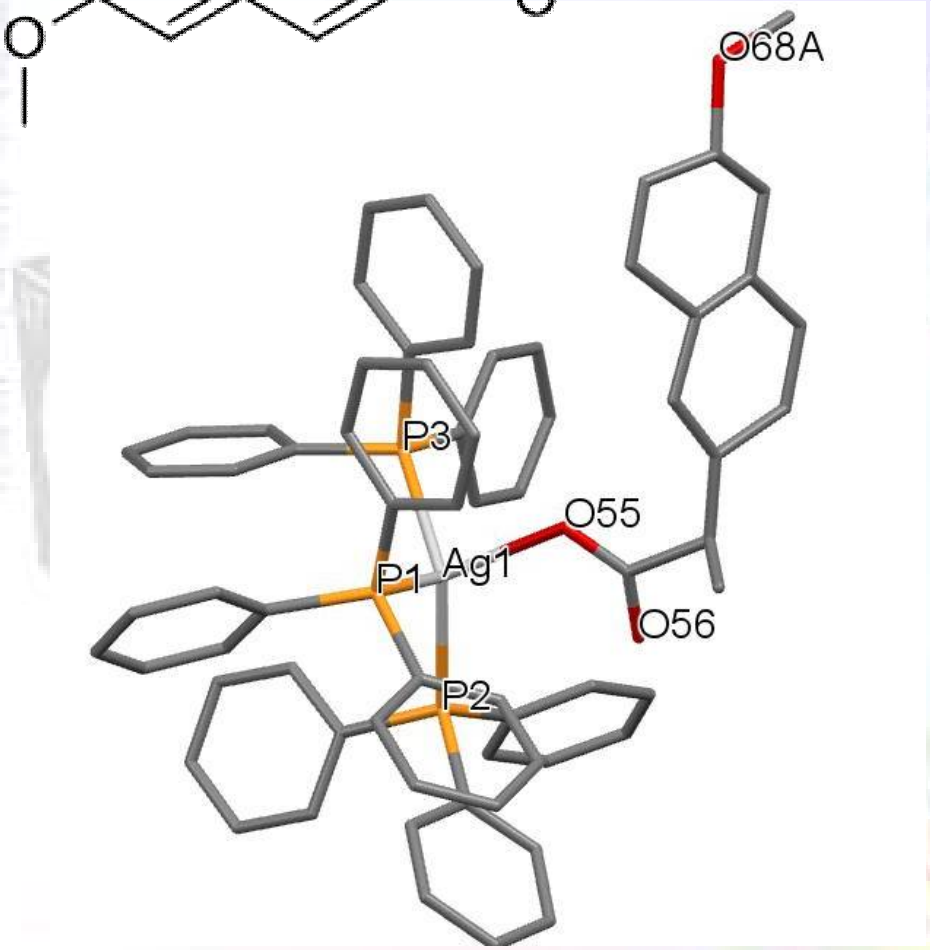
$[Ag(tmtp)_2(salH)]$

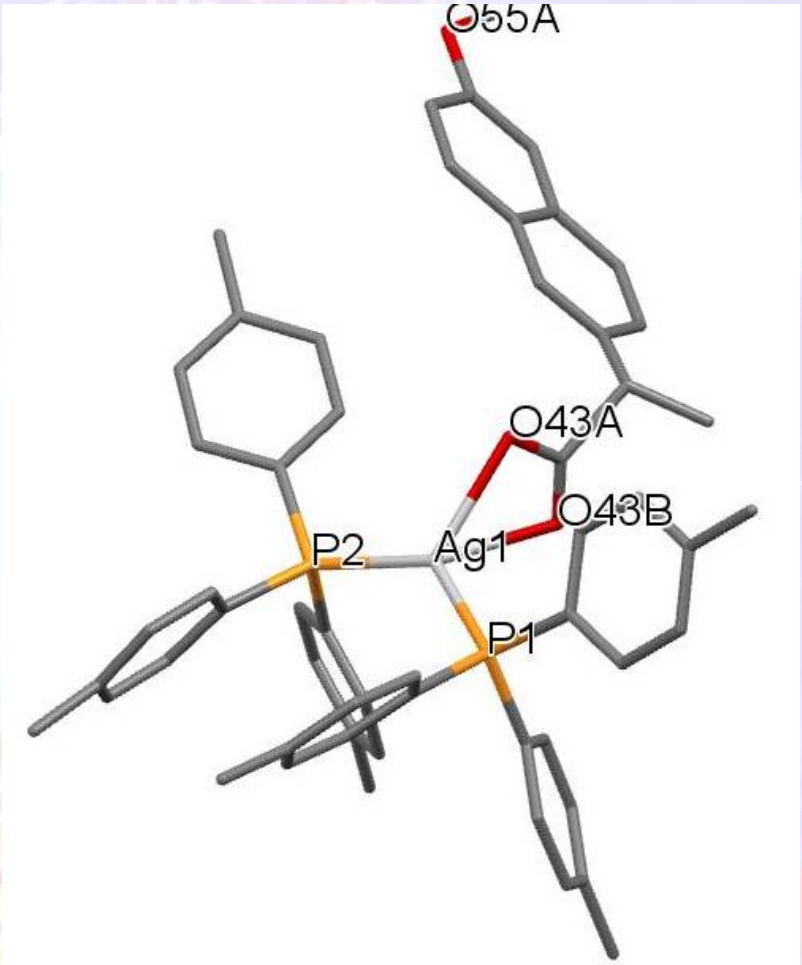


$[Ag(tptp)_2(p\text{-}Hbza)]$



Naproxen (NapH)



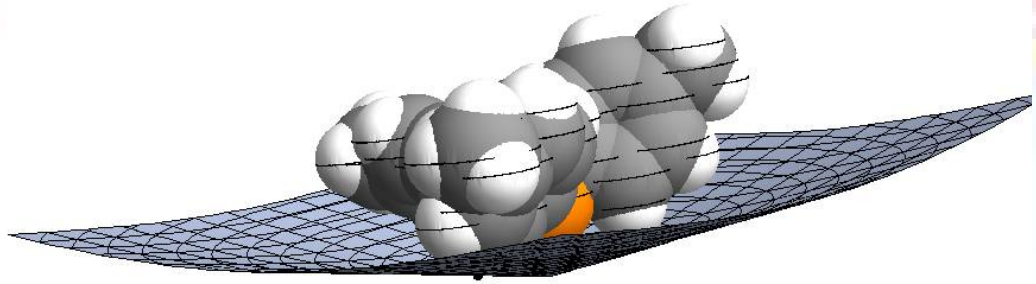


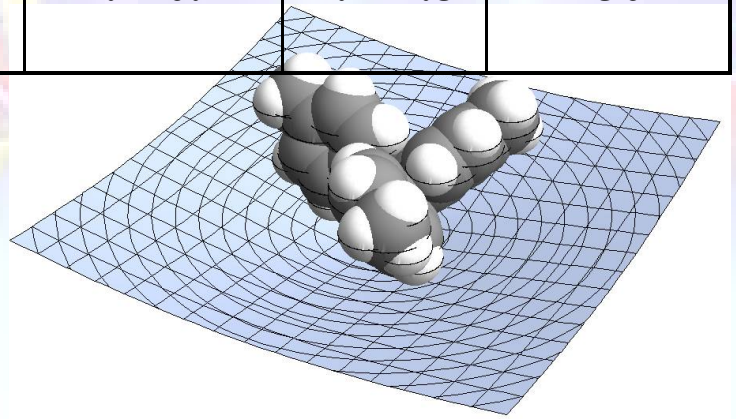
$\{[Ag(tpp)_3(napr)](H_2O)\}$ Ag1–P1 = 2.5302(10), Ag1–P2 = 2.4922(10), Ag1–P3 = 2.5068(10), Ag1–O55 = 2.373(3)

$[Ag(tptp)_2(napr)]$
Ag1–P1 = 2.4316(9), Ag1–P2 = 2.4149(9), Ag1–O43A = 2.375(3), Ag1–O43B = 2.547(3),

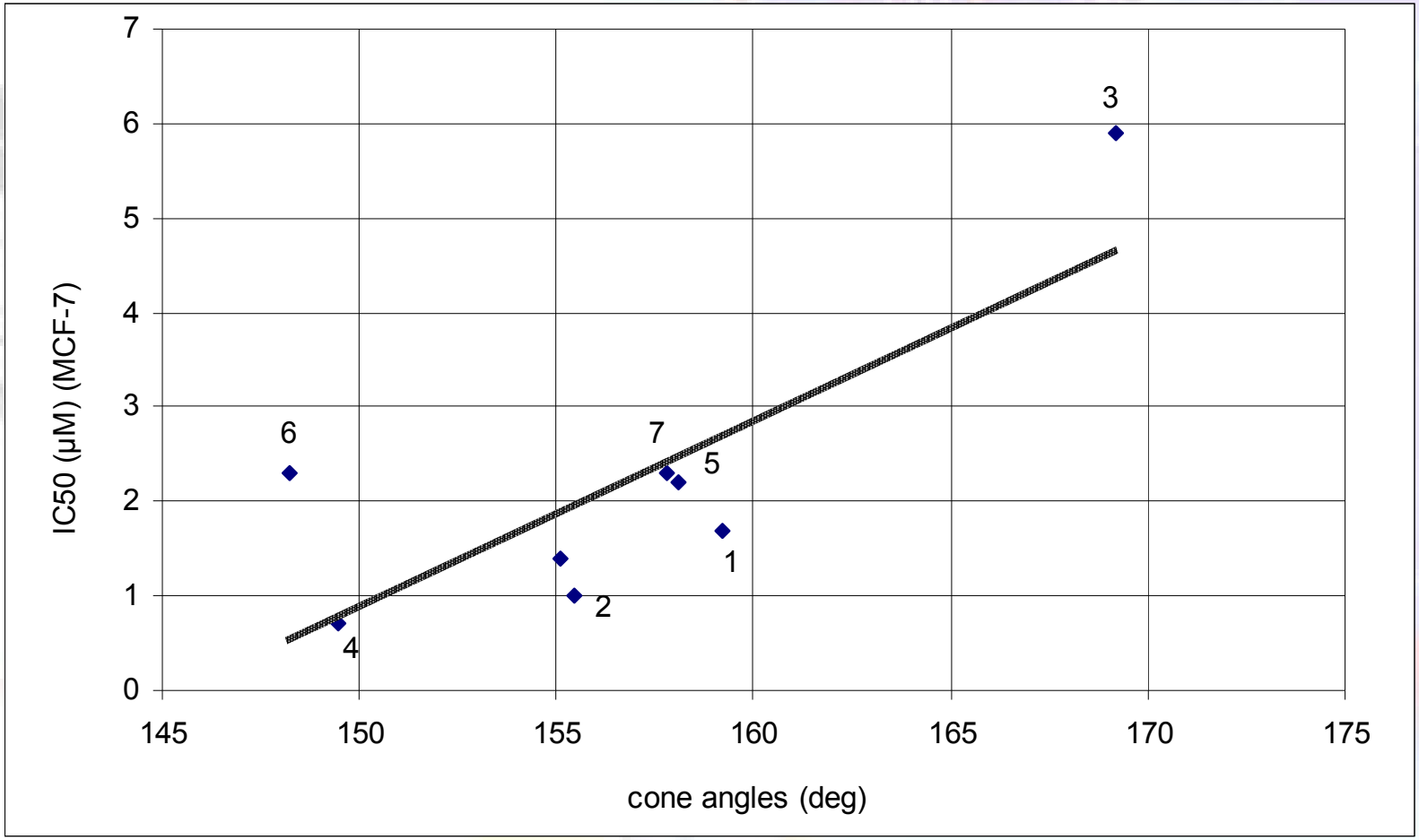
Bioactivity data recorded for mixed ligand silver(I) complexes with anti-inflammatory drugs or agents and arylphosphines.

Complexes	*Cone Angle deg*	*IC_{50} (μM) MCF-7*	*IC_{50} (μM) HeLa*	*K_b (M^{-1}) (×10^4)*	*IC_{50} (μM) LOX*
{[Ag(tpp)$_3$(asp)](dmf)}	148.2	2.3±0.3		11.0±2.8	7.2
[Ag(tptp)$_2$(salH)]	159.20	1.7±0.3	2.6±0.1	7.2±1.1	>30
[Ag(tptp)$_2$(*p*-Hbza)]	155.47	1.0±0.1	2.6±0.2	14.6±4.1	>30
[Ag(tmtp)$_2$(salH)]	169.16	5.9±0.8	16.6±1.7	5.3±0.8	>30
{[Ag(tpp)$_3$(napr)](H$_2$O)}	149.47	0.7±0.1	2.5±0.3	32.8±8.5	5.1
[Ag(tptp)$_2$(napr)]	158.08	2.2±0.2	1.2±0.1	4.7±1.8	>30

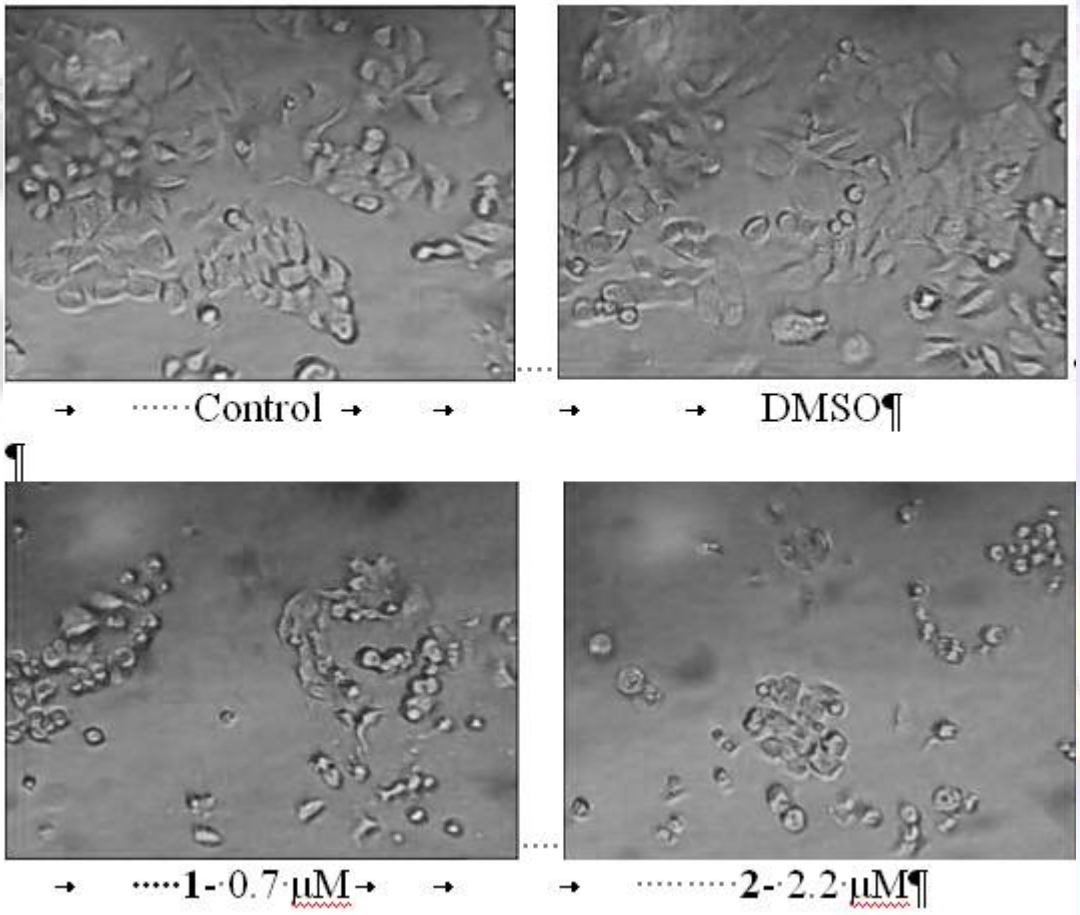


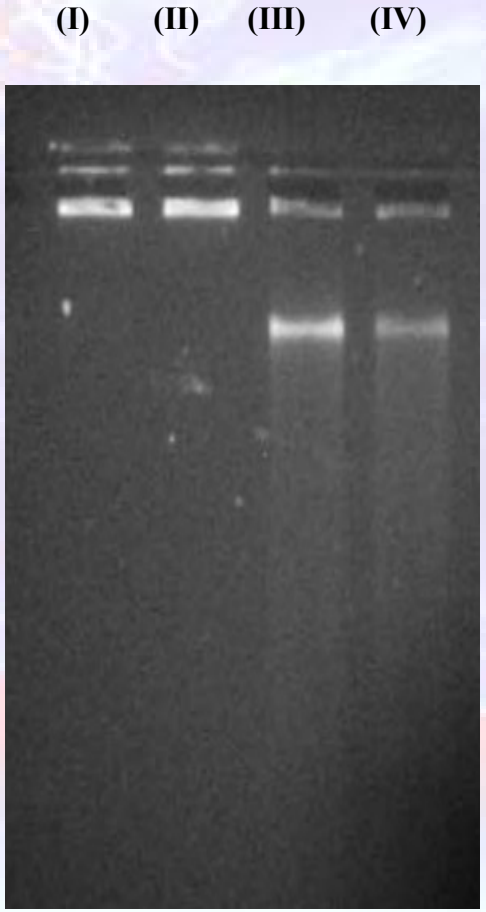


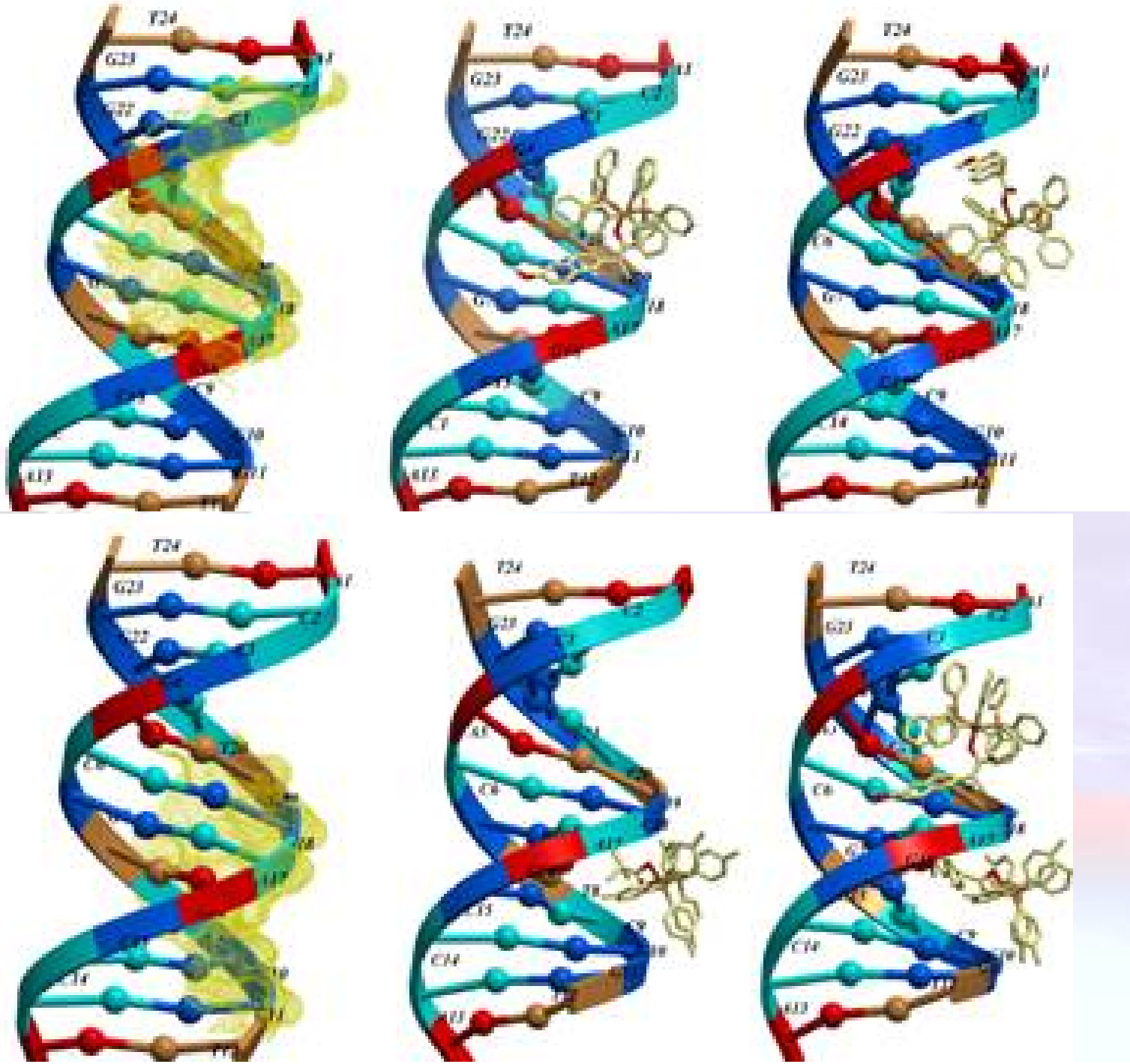
IC_{50} values vs cone angles of the complexes 1-3 and $\{[Ag(tpp)_3(napr)](H_2O)\}$ (4). $[Ag(tptp)_2(napr)]$ (5), $\{[Ag(tpp)_3(asp)](dmf)\}$ (6), $[Ag(tpp)_2(salH)]$ (7) and $[Ag(tpp)_2(p\text{-}Hbza)]$ (8) 3 ($y = 0.0169\ x^2 - 5.1569x + 394.71$; $R^2 = 0.9015$).



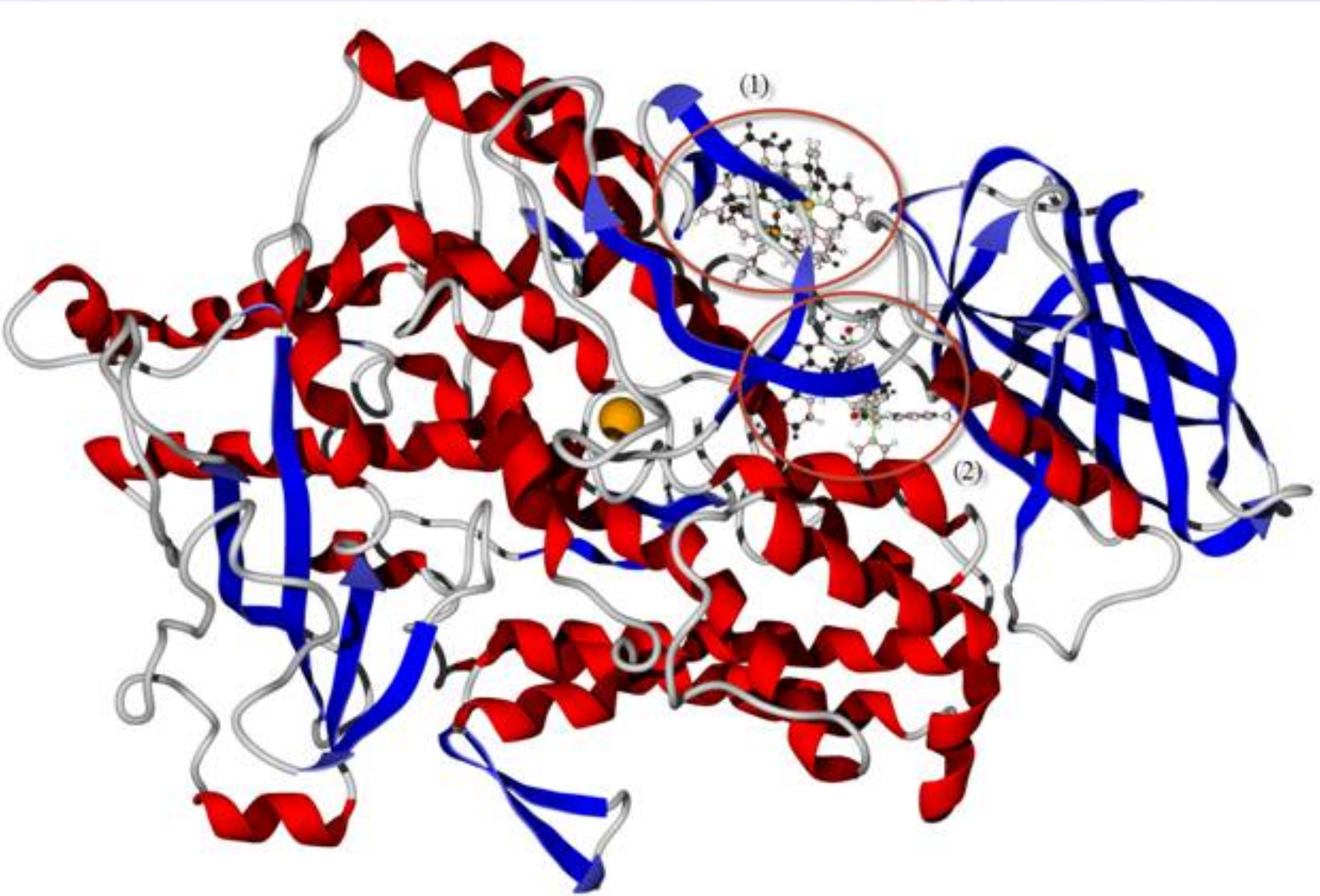
(**A**) Morphology of MCF-7 cells incubated by complexes **1-2**. (**B**) DNA electrophoresis of MCF-7 cells incubated with **1-2** for 48 hrs. (**I**: control; **II**: incubated with DMSO; **III**: incubated with **{[Ag(tpp)$_3$(napr)](H$_2$O)}** (0.72 μM); **IV**: incubated with **[Ag(tptp)$_2$(napr)]** (2.2 μM).

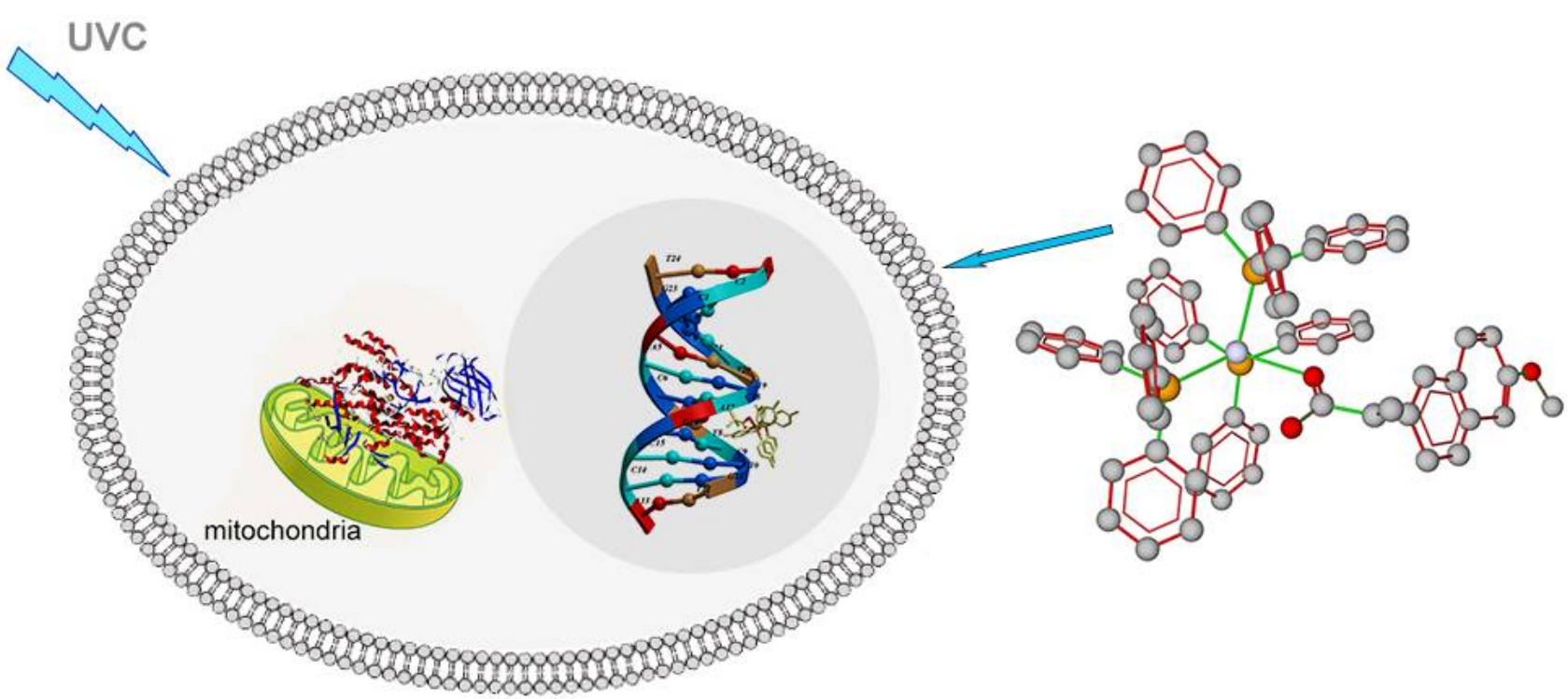






Theoretical binding pockets of **{[Ag(tpp)$_3$(napr)](H$_2$O)} and [Ag(tptp)$_2$(napr)]**.





The ID_{50} values of $\{[Ag(tpp)_3(napr)](H_2O)\}$ and $[Ag(tptp)_2(napr)]$ towards MCF-7 cells under irradiation (0.7 ± 0.1 (1), and 1.3 ± 0.2 (2) $\mu g\ ml^{-1}$ respectively) were decreased relative to the corresponding ones of the non-irradiated cells (0.8 ± 0.1 (1) and 2.1 ± 0.2 (2) $\mu g\ ml^{-1}$ respectively), by 13% (1) and 38% (2)

In vivo-Acute toxicity in wistar rats of silver(I) aspirin compound

Acute toxicity	Weight Day 0 (gr)	Weight Day 14 (gr)	ΔW (%)
Control	*170.8±14.6*	*192.4±17.7*	*12.6%*
Group 1 (0.5 mgr/kgr)	*178.8±9.5*	*200.4±8.0*	*12.1%*
Group 2 (5 mgr/kgr)	*168.0±5.6*	*191.8±5.6*	*14.2%*
Group 3 (50 mgr/kgr)	*180.2±11.2*	*199.2±10.4*	*10.5%*

1 single dose, scarified 14th day

No animal died

Group 0.5mgr/Kg
Lungs: Mild lesions

Group 5mgr/Kg
Liver: sinusoidal dilatation
Lungs: Mild hemorrhagic alveolar infiltration
and mild swelling in less than 10%

Group 50mgr/Kg
Liver: sinusoidal dilatation
Lungs: Mild compaction alveolar edema and mild to less than 10%
Kidney: mild edema degeneration in the cytoplasm of urinary tubules
Skin: Thinning Hairs

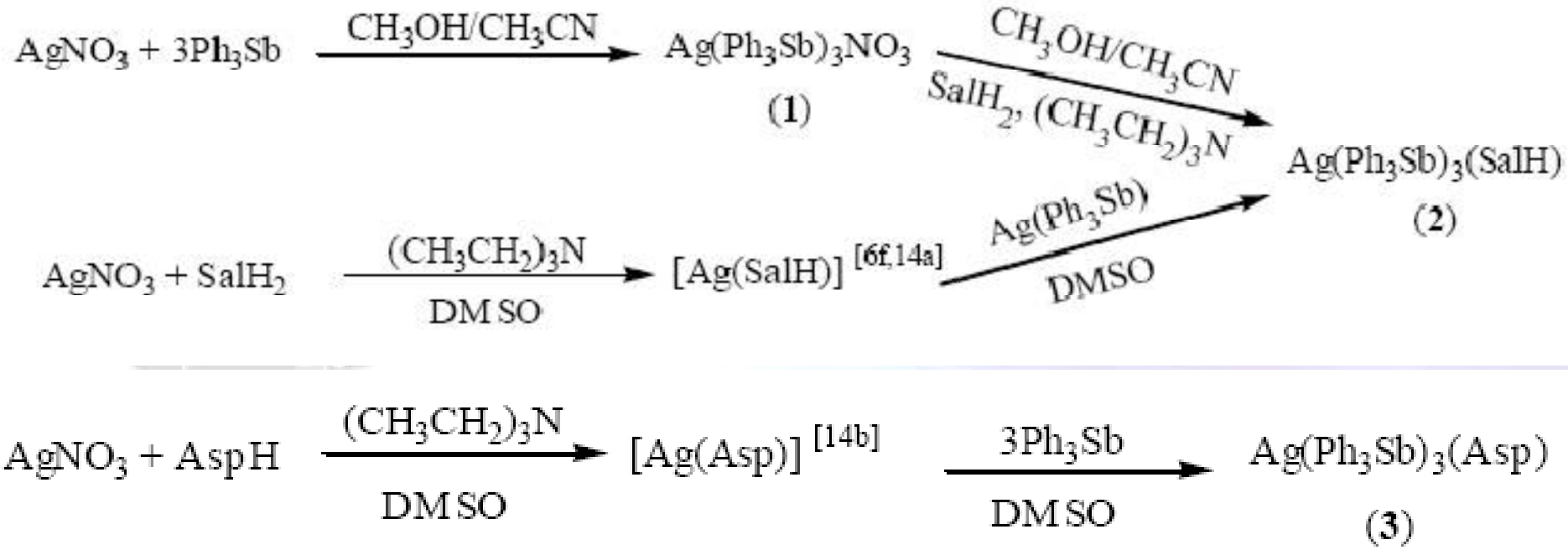
In vivo-Subchronic toxicity in wistar rats
Silver(I) Aspirin compound

Control	4 interval doses (1 dose per week) 90 days stay alive
Group 0.5mgr/kg	
Group 5mgr/kg	

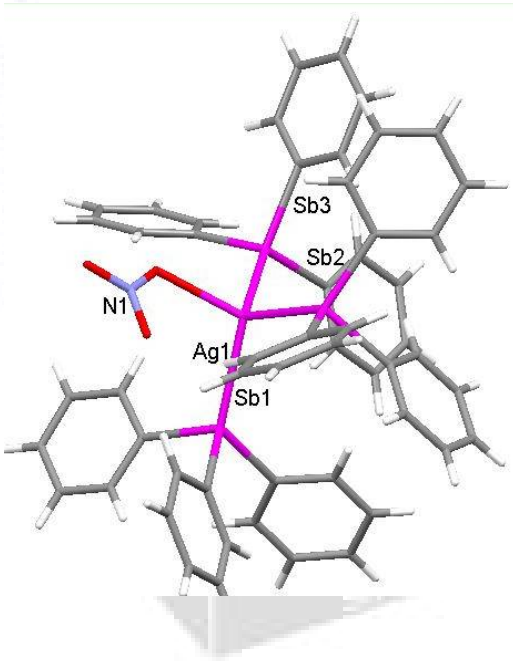
Lungs, kidney,

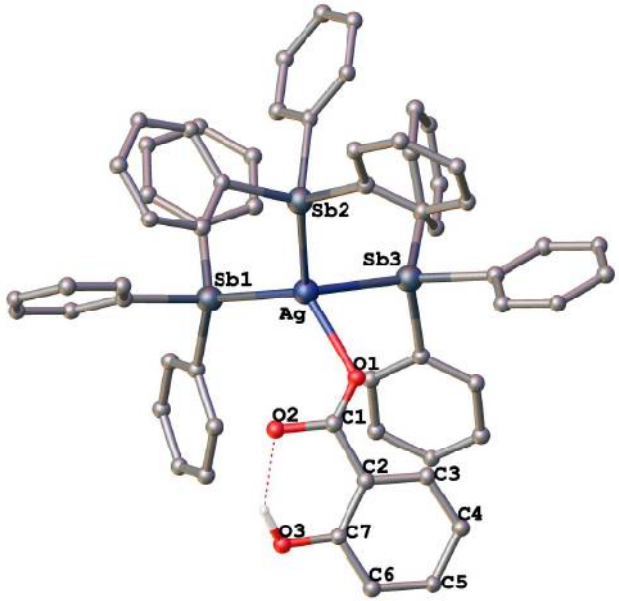
No animal died

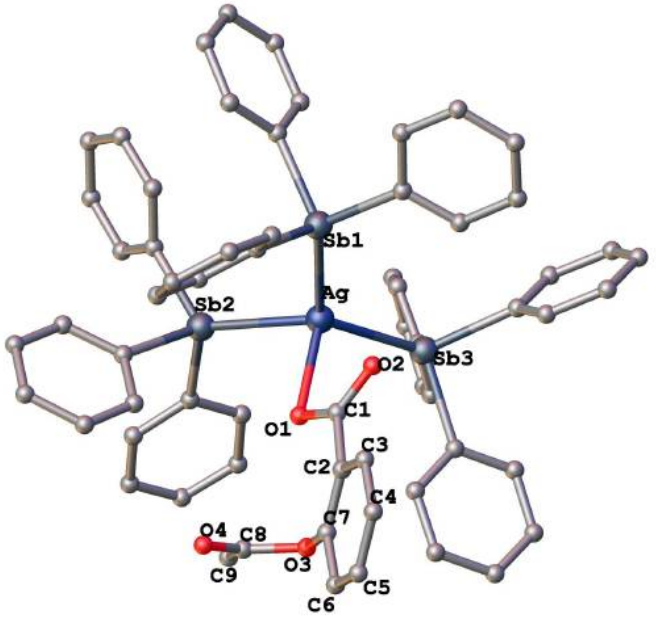
The compounds $\{Ag(Ph_3Sb)_3(NO_3)\}$ and two novel mixed metal Ag(I)-Sb(III) metallotherapeutics of the formulae $\{Ag(Ph_3Sb)_3(SalH)\}$ and $\{Ag(Ph_3Sb)_3(Asp)\}$ were prepared according to the reactiosn follows



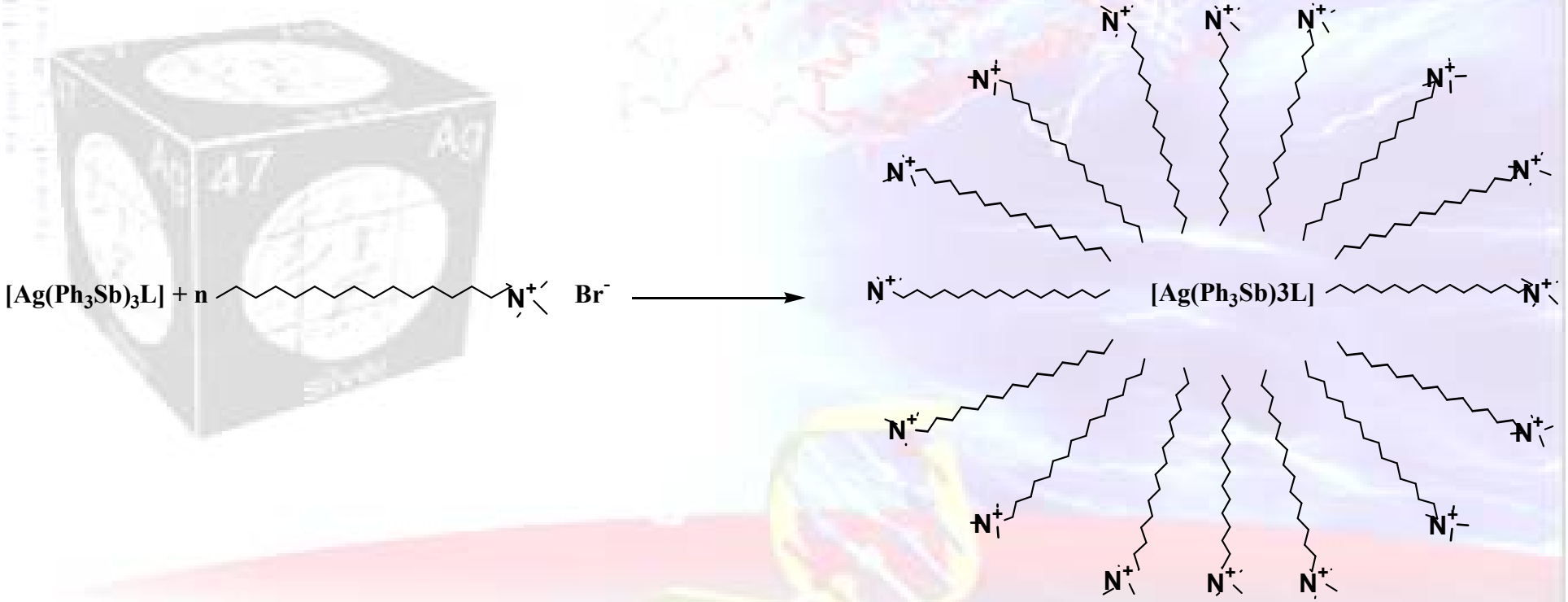
The compounds were characterized by spectroscopic methods (FTIR, Raman, ^{1}H,^{13}C-NMR, UV-Vis analysis and X-ray diffraction of mono-crystal.



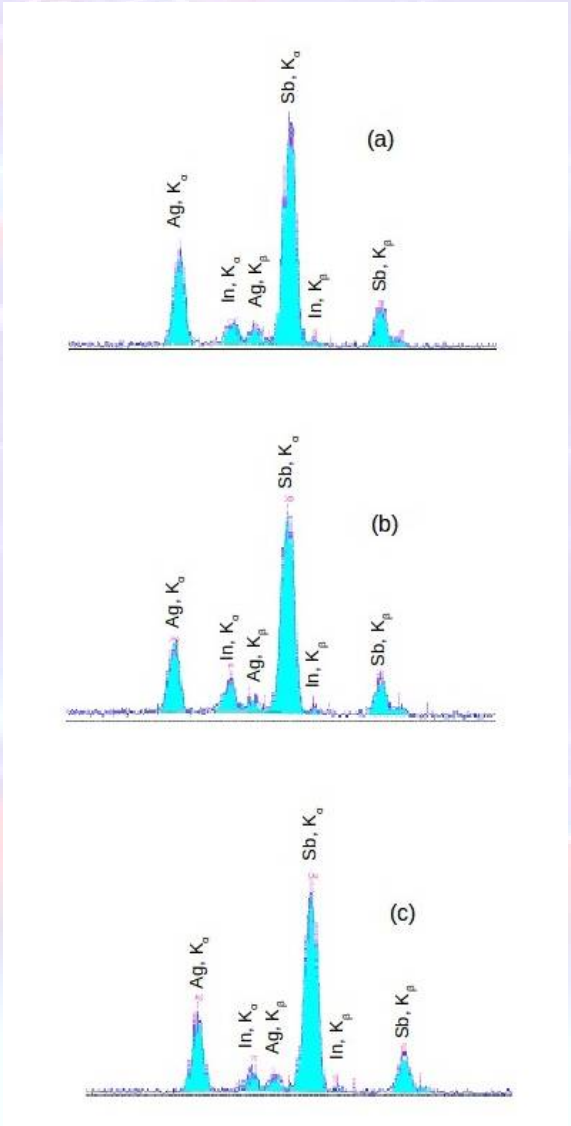




The micelles of the compounds with surfactant cetyltrimethylammonium bromide (CTAB) in the nano-particle size were prepared in accordance with the following reaction.



The micelles of compounds characterized X-ray powder diffraction (XRPD) analysis, X-ray fluorescence (XRF) spectroscopy, Energy-dispersive X-ray spectroscopy (EDX), conductivity, TG-DTA, and atomic absorption.



Atomic absorption analysis results

Micelle	m_{tot} (µg)	m_{Ag} (µg)	Percentage (%)
a	11600	6.77	0.66
b	9360	4.65	0.60
c	54170	76.3	1.76

Where, m_{tot}, the total mass of the micelle that was analysed, m_{Ag}, the detected mass of silver in the sample and Percentage (%), the percentage of the compound in the respective micelle.

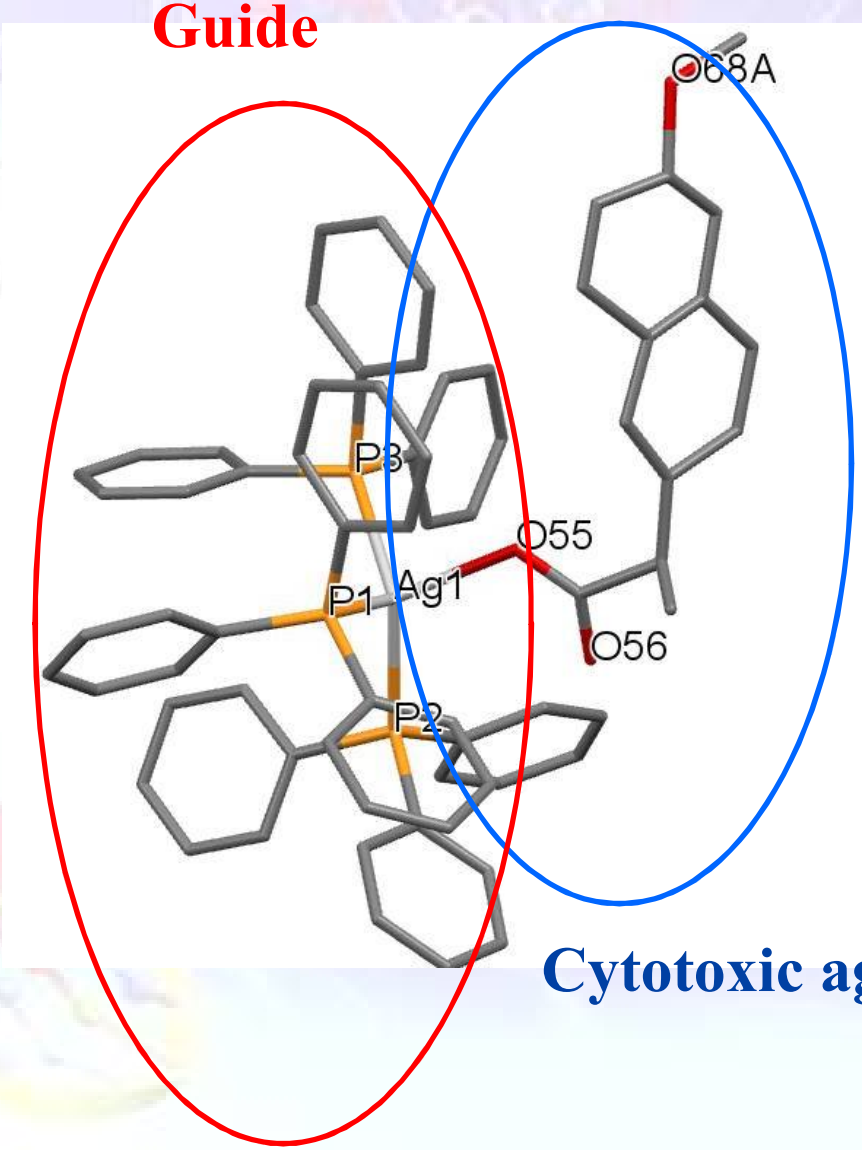
IC_{50} values for cell viability found for complexes 1–3 and their micelles a–c against MCF-7 (breast, ER positive), MDA-MB-231 (breast, ER negative) and the normal human lung cell line MRC-5 (normal human fetal lung fibroblast cells).

Compound	IC_{50} (μM)				
	MCF-7	MDA-MB-231	MRC-5	TPI MCF-7	TPI MDA-MB-231
$Ag(Ph_3Sb)_3(NO_3)$ (1)	3.05±0.11	5.67±0.17	4.36±0.44	1.42	0.77
Micelle a	0.045±0.01	0.042±0.01	0.070±0.01	1.56	1.66
$Ag(Ph_3Sb)_3$(SalH) (2)	3.19±0.07	7.26±0.18	5.03±0.12	1.58	0.69
Micelle b	0.048±0.01	0.044±0.01	0.062±0.01	1.29	1.41
$Ag(Ph_3Sb)_3$(Asp) (3)	5.88±0.39	14.86±0.86	4.75±0.82	0.81	0.32
Micelle c	0.103±0.01	0.157±0.01	0.263±0.05	2.55	1.67

Bioactivity data recorded for micelles a-c and silver(I) complexes with anti-inflammatory drugs or agents and arylphosphines.

Complexes	K_b (M^{-1}) ($\times 10^4$)	K_{app} (M^{-1}) ($\times 10^4$)	IC_{50} (μM) LOX
Micelle a	3.3±0.1	2239±178	8.4
Micelle b	10.0±0.1	2261±133	29.4
Micelle c	2.5±0.1	1128±250	>30
$[Ag(tptp)_2(salH)]$	7.2±1.1	0.6±0.2	>30
$\{[Ag(tpp)_3(asp)](dmf)\}$	11.0±2.8	-	7.2
$[Ag(tpp)_2(salH)]$	13.3±6.5	-	2.3
$[Ag(tmtp)_2(salH)]$	5.3±0.8	1.7±0.1	>30

Guide



Cytotoxic agent

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Πανεπιστήμιο Ιωαννίνων

22ο Πανελλήνιο Συνέδριο Χημείας Θεσσαλονίκη 2016

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Χημείας του Αριστοτέλειου
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Χημείας του
Πανεπιστημίου Κρήτης

Χημείας του Πανεπιστημίου
Πατρών

Χημείας του Πανεπιστημίου
Κύπρου