Research Article

Heterobimetallic Complexes: A Window into Medicinal Chemistry

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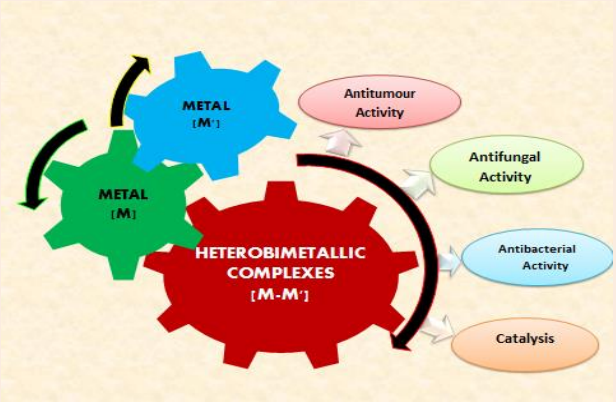
Abstract

The expansion of bioinorganic chemistry in the last decades gave a strong impetus to the development of coordination chemistry, and an enormous number of heterobimetallic complexes, with very interesting structures and properties, have been synthesized. Heterobimetallic complexes exhibit a fascinating range of applications in the medicinal chemistry due to their appealing biological properties. These complexes offer a diverse arena and their applications in medicine encompass treatment of several diseases that have continued to ravage mankind. This review article focuses on captivating field of heterobimetallic complexes owing to their sterling potential to exhibit remarkable biological activity. These complexes are fully characterized and their anticancer activity is assessed on a representative panel of human solid tumor cell lines. Selected examples are provided and discussed to accentuate the substantial progress made so far.



Keywords: Bimetallic complexes, heterobimetallic complexes, antifungal activity, antibacterial activity, antitumor activity

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Introduction

Over the last couple of years, the field of organometallic chemistry involving bimetallic complexes has grown and evolved at unprecedented rates. Recent publications largely highlight key advances on bimetallic complexes and on their chemically addressable applications in challenging areas like biology, medicine, catalysis, nanoscience, redox and photoactive materials, *etc*. This explosive expansion is mainly due to the unique ability of the metals that not only possess much of the interesting reactivity and spectroscopy within the periodic table, but they also engage in some of the most diverse binding modes and geometries [1] that allow the fine tuning of their chemical reactivity in terms of both kinetics (rate of ligand exchange) and thermodynamics (strengths of metal-ligand, redox potentials, etc.)[2]. In recent years, dinuclear complexes containing two different transition metal centers have received increasing attention owing to the presumption that their reactivity should vary substantially from that of monometallic complexes or homobimetallic complexes [3]. "We All Can Work; But Together We Win". The presence of two metals in the same molecule largely affects both the physical properties and the reactivity of the complexes**.** This is either due to the significant modification in the individual properties of the metals or in the development of novel characteristics, which do not occur in monometallic compounds [4]. The physical properties of these binuclear metal complexes (redox properties, florescence etc.) vary to a great extent. The reasons for investigating materials containing disparate metal centers are widespread, but common to many of them are applications in activating substrates arising from the bifunctionality of the differing metal atoms. Mononuclear metal complexes have historically received much attention (along with homodinuclear complexes, to some extent), but the excitement regarding heterodinuclear compounds emanates from reactivity hitherto unseen in their mono or homodinuclear counterparts; in other words, compounds containing two different metal centers exhibit synergistic reactivity that is different from that observed for compounds containing only one type of metal [5]. The advantages of early/late heterobimetallic complexes over monometallic or homobimetallic complexes are twofold:

1. Dative interactions between transition metal centers should have a dramatic effect on the redox activity of transition metals, facilitating reduction of the late transition metal and ideally leading to substrate reduction/activation at mild over potentials. Metal-metal interactions provide a unique mechanism for storing redox equivalents and tuning redox properties.
2. Unlike bimetallic complexes featuring identical or similar metals, the bonds between metals in early/late heterobimetallics are more polar in nature, with the electron-rich late metal center donating electron density to the empty d orbital(s) on the electron-deficient early metal center. Thus, heterolytic activation of substrates across the M→M′ bond in early/late heterobimetallic complexes is a promising reaction pathway [3].

Exploits in heterobimetallic chemistry have renewed hope in the design of drugs that will combat ailments, restore potency by overcoming drug resistance which have bedeviled well-known organic drugs, and of course, tackling the issue of toxicity. Interest in heterobimetallic complexes has seen explosive growth in the past few years, with an enormous number of compounds synthesized containing metal ions from throughout the periodic table. This short review will x-ray the trend in the search for varied biological activity of heterobimetallic complexes and the hope of this interdisciplinary research area in medicine.

Heterobimetallic Complexes as Antimicrobial Agents

Transition metal complexes offer various potential advantages [6] for the design of therapeutic agents, however the major advantage of metal-based drugs over purely organic drugs is the ability of metal ions to vary coordination number, geometry and redox states [7].The growing interest in biochemical applications and an interest in better fungicides and bactericides have prompted to synthesize heterobimetallic complexes with sterling antimicrobial activity. Since emergence of resistance to antimicrobial drugs has become an issue of public health concern, it is thus pertinent to develop new agents with antimicrobial activities to curb infections by these resistant strains. Since some of these metal complexes showed better antimicrobial activity than the parent drugs, they have potential to be used as antibacterial and antifungal agents and this should be explored.

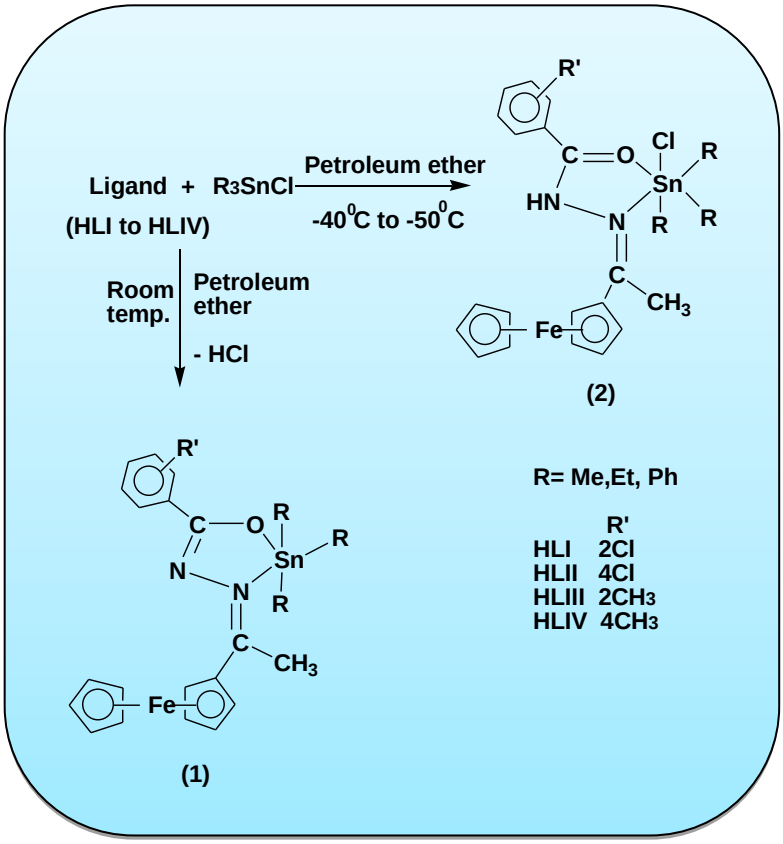

Figure 1 Complexes synthesized by reaction of triorganotin (IV) chloride with ferrocenyl aroylhydrazone at different temperature

Iron-Tin complexes

Organotin compounds show a wide spectrum of biological activity [8, 9] and the activity is essentially determined by the number and nature of the organic moiety bound to tin atom. Mono and diorganotin complexes are biologically less active, whereas triorganotin complexes usually act as powerful biocides. Triorganotin compounds, R_3SnX, are known for having specific action on mitochondrial oxidative phosphorylation; the activity is independent of the X group[13],when R= Me or Et, the compounds are most toxic towards mammals but when R= n-octyl, the compound has low activity. Taking this into consideration, Malhotra et al. reported the reactions of triorganotin (IV) chloride with ferrocenyl aroylhydrazone derived from condensation of acetylferrocene and aromatic acidhydrazide yield heterobimetallic penta and hexacoordinated organotin(IV) complexes of the type $R_3Sn(L)$ (1) and $R_3Sn(HL)Cl$ (2) (where R= Me, Et or Ph ; HL = ferrocenyl aroylhydrazone) (**Figure 1**) [10]. These complexes were evaluated for antifungal activity against *Alternaria alternate*, *Fusarium oxysporum* and *Rhizoctonia solani*, as well as antibacterial activity against gram negative, (*Escherichia coli*) and gram positive bacilli (*Bacilli subtilis*) at 28º C. Triphenyltin(IV) complexes were found to be more potent than the methyl or ethyl counterpart. The triorganotin complexes isolated at low temperature, i.e. $R_3Sn(HL)Cl$, were more active than the complexes isolated at room temperature, i.e. $R_3Sn(L)$, indicating that complexes having reactive halogen atom tend to hydrolyse to form compounds that have modified activity spectrum.

Palladium/Platinum-Tin complexes

Numerous studies on organotin(IV) complexes have been carried out to explore their biological properties against bacterial, fungal strains, and cancer cells line (Hadjikakou & Hadjiliadis, 2009; Hadjikakou, Ozturk, Xanthopoulou, & Zachariadis, 2008)[11, 12]. Recently, significant attention has been focused on the DNA binding properties of dithiocarbamate metal complexes among which Pd(II) and Pt(II) complexes of dithiocarbamates have gained special interest due-to-their potential antitumor properties (Islami-Moghaddam, Mansouri-Torshizi, Divsalar, & Saboury, 2009; Mansouri-Torshizi, Moghaddam, Divsalar, & Saboury, 2009)[13]. Keeping in view, wide scope and the applications of organotin(IV)/Pd(II) complexes, Hussain et al. synthesized four heterbimetallic derivatives of the type, $[R_2(Cl)SnL]PdCl_2$ (R= n-Bu: 3) / $[R_3SnL]PdCl_2$ (R= Me: 4; n-Bu: 5; Ph: 6) where L= 4-(2- hydroxyethyl) piperazine-1-carbodithioic acid by refluxing 4-(2- hydroxyethyl) piperazine-1-carbodithioic acid with R_2SnCl_2/R_3SnCl in 1:1 M/L ratio and then stirring with $PdCl_2$ at room temperature (**Figure 2**).

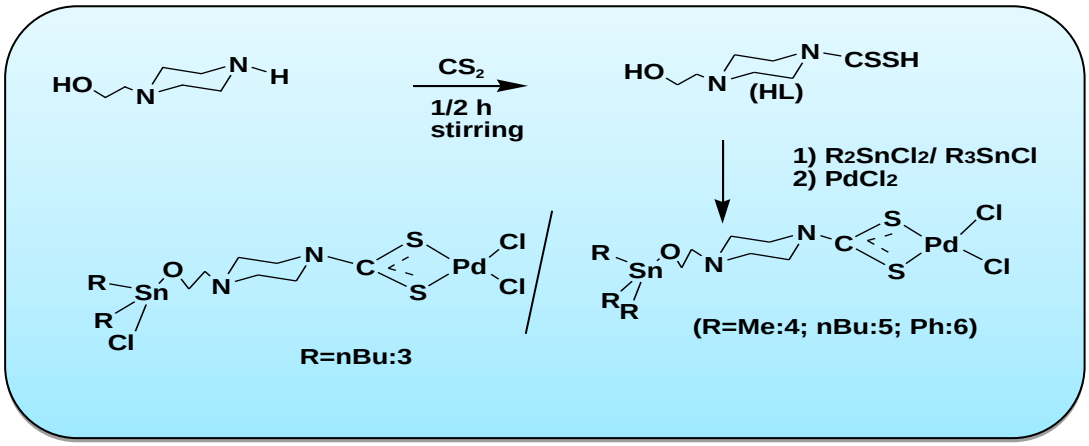

Figure 2 Synthetic route for synthesis of heterobimetallic (Sn, Pd) complexes with 4-(2- hydroxyethyl) piperazine-1-carbodithioic acid (HL)

The complexes demonstrated the 4-coordinated geometry around Sn(IV) and Pd(II) in both the solid and solution states [14]. These complexes were tested for their interaction with alkaline phosphates enzyme (ALPs) and salmon sperm DNA (SS-DNA). They were screened against various strains of bacteria/fungi and showed significant antimicrobial activities as compared to free ligand. The *in vitro* hemolytic activity showed that average lysis of human red blood cells was significantly lower as compared to Triton-X 100 (positive control, 100% lysis).

Nickel-Copper complexes

Since acylhydrazones are strong biologically active compounds (Mohan et al. 1988; Maiti and Ghosh 1989) [15, 16], their heterobimetallic complexes may have potential uses as fungicides and bactericides. Singh et al. synthesized and characterized a number of nickel (II) tetrathiocyanato dicuperate (I) complexes with some acylhydrazones and studied their antifungal and antibacterial activities. Heterobimetallic complexes of the type $Ni[Cu(SCN)_2]_2.L$ (7) (where L= acetophenone benzoylhydrazone (abh), acetophenone isonicotinoyl hydrazine (ainh), acetophenone salicyloylhydrazone (ash), acetophenone anthraniloylhydrazone (aah), p-hydroxy acetophenone benzoylhydrazone (phabh), p-hydroxy acetophenone isonicotinoyl hydrazine (phainh), p-hydroxy acetophenone salicyloylhydrazone (phash), p-hydroxy acetophenone anthraniloyl hydrazine (phaah)), were synthesized and characterized [17]. These complexes are polymeric, insoluble in common organic solvents and are nonelectrolytes. X-ray powder diffraction parameters for $Ni[Cu(SCN)_2]_2$.ash and $Ni[Cu(SCN)_2]_2$.phash correspond to orthorhombic and tetrahedral crystal lattices, respectively, for these complexes. The complexes show a significant antifungal activity against *Rizoctonia*, *Stemphylium* and *Aspergillus sp*. and antibacterial activity against *Clostridium* and *Pseudomonas sp*. The metal complexes were found to be more active than the ligands.

The antifungal data (**Table 1**) indicate that the complexes show a significant activity against *Rizoctonia, Stemphylium* and *Aspergillus sp.* at concentrations of 0.5, 1.0 and 1.5 mg mL^{-1}. However, they are more effective against *Rizoctonia* and *Stemphylium sp.* as compared to *Aspergillus sp*. Their activity is enhanced at higher concentrations of the compounds. The ligand was found to exhibit lower activity than their complexes [18]. The effectiveness of the complexes generally varies in the following order of fungal species:

Rizoctonia sp. > Stemphylium sp. > Aspergillus sp.

Table 1 Antifungal activity of nickel (II) tetrathiocynato dicuprate (I) complexes with some acyl hydrazones [Inhibition of spore germination (%)]

Compounds	Rizoctonia sp.($mgmL^{-1}$)			Aspergillus sp.($mgmL^{-1}$)			Stemphylium sp.($mgmL^{-1}$)		
	0.5	1.0	1.5	0.5	1.0	1.5	0.5	1.0	1.5
abh	46	64	80	23	40	47	78	80	89
ainh	60	94	95	34	36	38	67	73	85
ash	62	69	79	33	39	44	58	64	79
aah	39	77	84	32	40	48	82	84	86
phabh	44	45	78	34	64	71	61	62	64
phainh	76	92	95	35	60	66	71	89	95
phash	67	71	82	36	40	48	75	83	84
phaah	33	61	65	25	27	30	57	75	85
$Ni[Cu(SCN)_2]_2$.abh	76	81	83	32	48	54	88	89	92
$Ni[Cu(SCN)_2]_2$.ainh	77	80	86	48	59	62	74	81	88
$Ni[Cu(SCN)_2]_2$.ash	94	96	98	37	51	56	68	72	82
$Ni[Cu(SCN)_2]_2$.aah	89	95	96	49	68	72	87	91	92
$Ni[Cu(SCN)_2]_2$.phabh	69	71	88	34	72	86	72	79	82
$Ni[Cu(SCN)_2]_2$.phainh	86	88	97	52	68	73	77	90	98
$Ni[Cu(SCN)_2]_2$.phash	65	78	89	42	48	55	78	84	89
$Ni[Cu(SCN)_2]_2$.phaah	72	77	82	36	47	60	72	79	92

The antibacterial activity data (**Table 2**) show a moderate activity against *Clostridium sp*. (gram +ve) and *Pseudomonas sp*. (gram -ve) at the concentrations of 1.0 and 2.0 mg mL^{-1}. The metal complexes show higher activity than the ligands and their activity increases with increase in concentration [19]. The activity has been compared with the activity of a common standard antibiotic ampicillin and a percentage activity index was calculated for the complexes. The percentage activity index data indicate that ainh is the most active ligand among all the ligands.

Table 2 Antibacterial activity of nickel(II) tetrathiocynato dicuprate(I) complexes with some acyl hydrazones

Compounds	Diameter of inhibition (mm)		Activity index(%)		Diameter of inhibition (mm)		Activity Index(%)	
	Clostridium sp. (mg mL^{-1})				*Pseudomonas sp.* (mg mL^{-1})			
	1.0	**2.0**	**1.0**	**2.0**	**1.0**	**2.0**	**1.0**	**2.0**
abh	2	4	14.3	25.0	2	3	11.1	16.7
ainh	4	6	28.6	37.5	3	6	16.7	33.3
ash	2	3	14.3	18.8	2	4	11.1	22.2
aah	4	5	28.6	31.2	5	6	27.8	33.3
phabh	3	4	21.4	25.0	2	2	11.1	11.1
phainh	2	4	14.3	25.0	2	2	11.1	11.1
phash	2	2	14.3	25.0	2	3	11.1	16.7
phaah	3	3	21.4	18.8	3	4	16.7	22.2
$Ni[Cu(SCN)_2]_2$.ainh	5	7	35.7	43.7	6	8	33.3	44.4
$Ni[Cu(SCN)_2]_2$.ash	7	10	50.0	62.5	5	9	27.8	50.0
$Ni[Cu(SCN)_2]_2$.aah	8	9	57.1	56.2	6	8	33.3	44.4
$Ni[Cu(SCN)_2]_2$.phabh	6	8	42.8	50.0	5	7	27.8	38.8
$Ni[Cu(SCN)_2]_2$.phainh	7	8	50.0	50.0	6	8	33.3	44.4
$Ni[Cu(SCN)_2]_2$.phash	7	8	50.0	50.0	7	8	38.9	44.4
$Ni[Cu(SCN)_2]_2$.phaah	9	12	64.3	75.0	8	10	44.4	55.5
Ampicillin(standard)	14	16	100.0	100.0	18	18	100.0	100.0

Copper/Nickel/Cobalt-Tin complexes

The potential of the metal complexes to act as therapeutic agents is already well established and notable are cobalt, copper and nickel metal ions. Cobalt and copper being redox active play a key role in several biological processes and have exhibited pronounced antibacterial and antitumor properties [20, 21]. Tabassum et al. reported the heterobimetallic complexes containing $Co\text{-}Sn_2$, $Cu\text{-}Sn_2$ and $Ni\text{-}Sn_2$ metallic cores derived from indole-3-acetic acid and 1,10-phenanthroline [22] (**Figure 3**). Indole-3-acetic acid – a phytohormone of the auxin series is a substance of multifunctional biological significance, and indole ring is a component of tryptophan, tryptamine, serotonin, gramine and Hoechst-33258 etc. that have been extensively used in medicinal preparations.

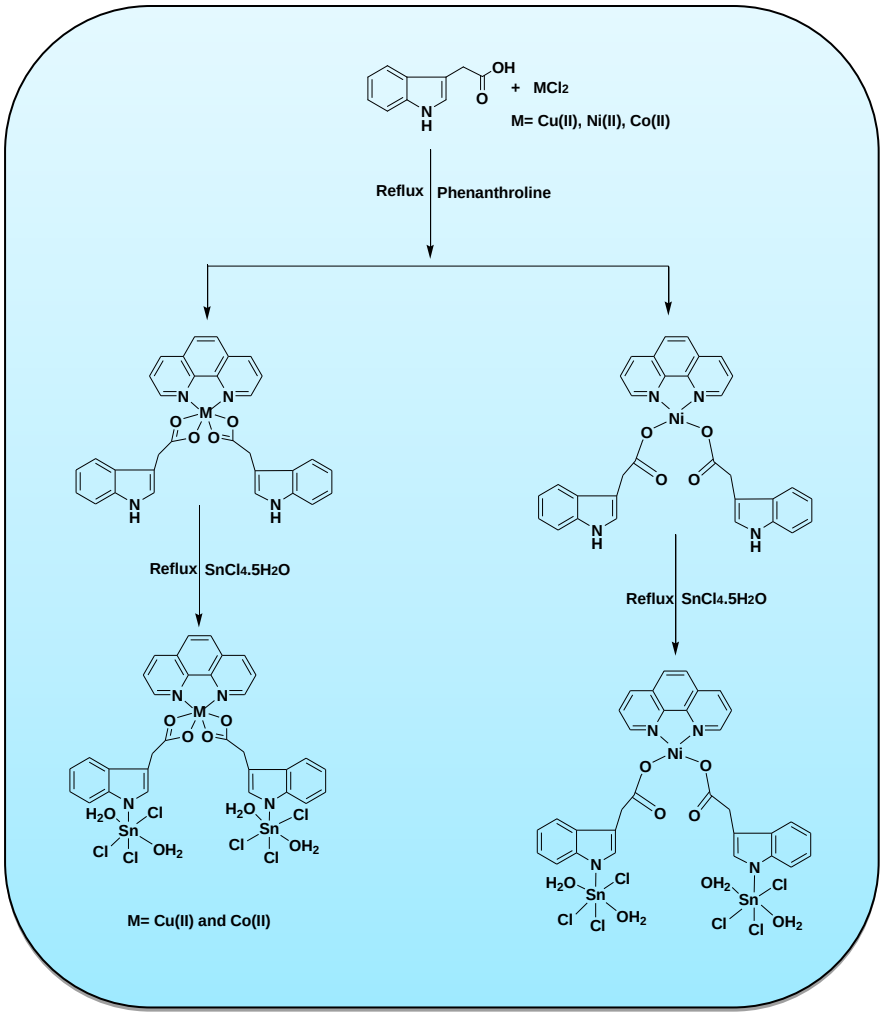

Figure 3 Synthetic route to monometallic and heterobimetallic complexes using phenanthroline and indole-3-acetic acid

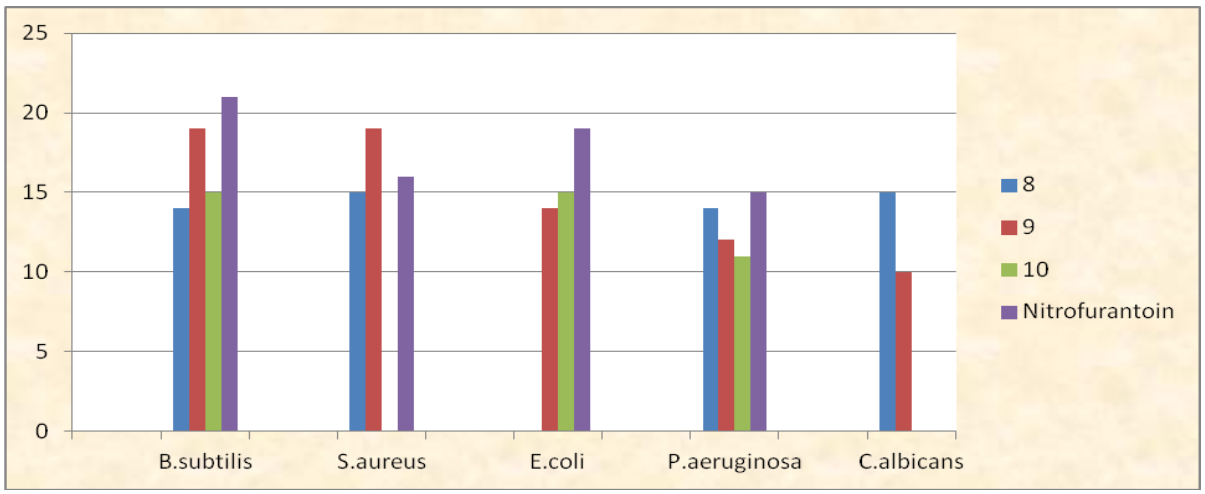

Figure 4 Antibacterial activity of complexes 8-10 against (1) *B. subtilis*, (2) *S. aureus*, (3) *E. coli* and (4) *P. aeruginosa*. (5) *C. albicans*. Standard = Nitrofurantoin. Inhibition zone in mm (100 µg/ disc)

The heterobimetallic complexes 8-10 {[$C_{32}H_{30}O_8N_4NiSn_2Cl_6$], [$C_{32}H_{30}O_8N_4CuSn_2Cl_6$] and [$C_{32}H_{30}O_8N_4CoSn_2Cl_6$]} were screened for the in vitro antibacterial activity against Gram-positive *Bacillus subtilis* [MTCC 121], *Staphylococcus aureus* [NRRLB 767] and Gram-negative *Escherichia coli* [K 12], *Pseudomonas aeruginosa* and in vitro antifungal activity against *Candida albicans* (**Figure 4**).

All the complexes exhibited varying degree of inhibitory effects on the growth of bacterial and fungal strains. Among all the complexes, complex 9 shows activity against *B. subtilis* and *S. aureus* with zone diameter 19 and 19 mm, respectively (**Figure 5**). Furthermore the complex 8 exhibited pronounced activity against Gram-positive bacteria *S. aureus* and Gram-negative bacteria *P. aeruginosa* with zone diameter 15 and 14 mm respectively. The other complex 10 showed moderate activity against *E. coli* and *P. aeruginosa* with zone diameter 15 and 11 mm respectively. Interestingly complex 8 was found to exhibit significant antifungal activity against the *C. albicans*. The results revealed that complex 9 was found to be more active as antibacterial than as antifungal as it shows a good zone of inhibition against all tested bacterial isolates. This is due to the enhanced penetration of complexes into the lipid memberanes [23]

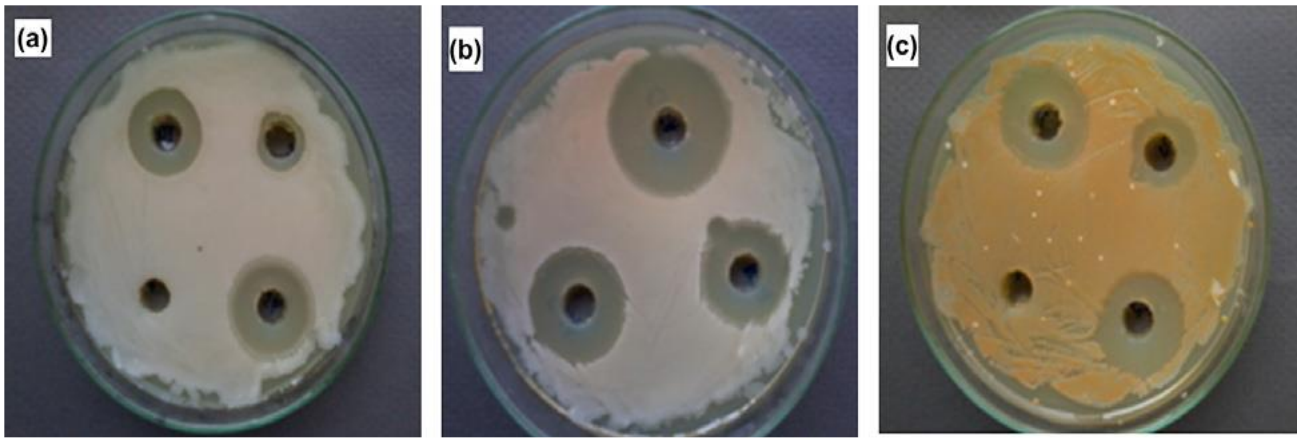

Figure 5 Bacterial activity against *S. aureus* of (a) complex 8 (b) complex 9 and (c) complex 10.

Zinc-Tin complexes

Complexes of organic compounds of tin (IV) and zinc (II) have been intensively studied in view of their potential biological activity, reactivity, and industrial applications [24]. In particular, such complexes may act as antiviral and antineoplastic agents, bactericides, fungicides, marine antifouling paints, surface disinfectants, wood preservatives; they are used in organic synthesis and fingerprint detection as well [25]. A series of new heterobimetallic complexes of zinc and tin with 4-aminophenylacetic acid has been prepared by Shahzadi et al. along with their composition and structure in solid state and in solution elucidated by elemental analysis, IR, ^{1}H NMR, and ^{13}C NMR spectroscopy (**Figure 6**). IR spectroscopy results have confirmed the bidentate nature of the ligand, its molecules being arranged in planar square [Zn(II)] and trigonal bipyramid [Sn(IV)] around the metal ions. The complexes containing both Sn(IV) and Zn(II) have proved to be better antimicrobial agents as compared to the Zn-only analog [26].

Antibacterial activity of the ligand, the complexes, and the reference drug was tested against Gram-positive and Gram-negative bacterial strains: *Escherichia coli, Bacillus subtilis, Pasturella multocida*, and *Stephlococcus aureus*. The measured growth inhibition zones are listed in **Table 3**. The complexes exhibited significantly higher antibacterial activity as compared to the free ligand. The ligand and Zn product showed no or little activity against the tested bacterial strains. Complex 16 ($C_{35}H_{34}O_6N_2S_2ZnSn$) revealed the highest activity against all the strains, only slightly lower than that of the reference drug. Thus, the complex with Zn only was not efficient as antibacterial drug, but its coordination with Sn (IV) enhanced the antibacterial activity significantly. The complexes containing methyl and phenyl groups showed highest inhibitory effect on bacteria growth [27]. Therefore, the tested bimetallic complexes can be potentially used as bactericides.

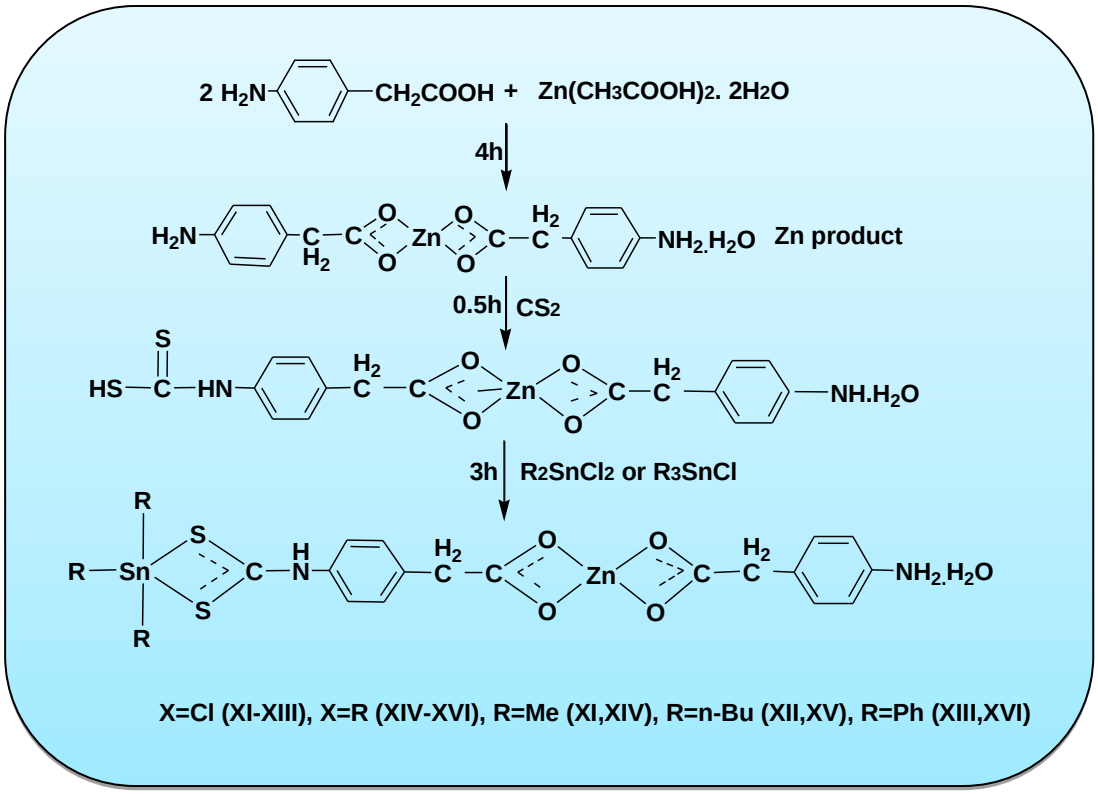

Figure 6 Scheme for the preparation of heterobimetallic complexes of Zn and Sn with 4-amino-phenylacetic acid

Table 3 The antibacterial activity data of Zn(II) and Sn(IV) complexes with 4-aminophenylacetic acid (Inhibition zone, mm)

	Compound	*B. subtilis*	*P. multocida*	*S. aureus*	*E. coli*
HL	($C_8H_9O_2N$)	*	*	*	1419±11
Zn product	($C_{16}H_{20}O_6N_2Zn$)	*	*	*	2019±11
XI	($C_{19}H_{25}O_6N_2S_2ClZnSn$)	2519±12	2119±12	1819±11	19±1
XII	($C_{25}H_{37}O_6N_2S_2ClZnSn$)	1819±11	2419±12	2419±12	*
XIII	($C_{29}H_{29}O_6N_2S_2ClZnSn$)	21±2	2319±12	2819±12	2319±12
XIV	($C_{20}H_{28}O_6N_2S_2ZnSn$)	2719±12	2319±12	1919±11	2019±11
XV	($C_{29}H_{46}O_6N_2S_2ZnSn$)	1919±11	2519±12	2019±11	2819±12
XVI	($C_{35}H_{34}O_6N_2S_2ZnSn$)	2819±12	2719±12	2919±12	3119±12
Ampicillin		3319±12	2919±12	3919±12	4019±12

*No activity

The antifungal activity of the ligand, the complexes, and the reference drug was tested against selected fungal strains: *Alternaria alternata, Ganoderma lucidium, Aspergilus flavus and Aspergilus niger*. The measured growth inhibition zones are listed in **Table 4**. In general, all the tested compounds revealed lower antifungal activity against *Aspergilus flavus and Aspergilus niger* as compared to that against *Alternaria alternate* and *Ganoderma lucidium*. The observed growth inhibition by complexes 11, 14–16, and by the free ligand was roughly similar, however somewhat weaker than that in the case of reference drug. Therefore, all the tested complexes can be potentially used as fungicides.

Table 4 The antifungal activity data of Zn (II) and Sn (IV) complexes with 4- aminophenylacetic acid (Inhibition zone, mm)

Compound		***G. lucidium***	***A. alternata***	***A. flavus***	***A. niger***
HL	($C_8H_9O_2N$)	2619±12	2619±12	2419±12	2819±12
Zn product	($C_{16}H_{20}O_6N_2Zn$)	1919±11	2219±11	*	*
XI	($C_{19}H_{25}O_6N_2S_2ClZnSn$)	1919±11	1419±11	2719±12	2519±12
XII	($C_{25}H_{37}O_6N_2S_2ClZnSn$)	1919±11	2119±12	*	*
XIII	($C_{29}H_{29}O_6N_2S_2ClZnSn$)	2019±11	1719±12	2819±12	*
XIV	($C_{20}H_{28}O_6N_2S_2ZnSn$)	2119±11	1719±11	2819±12	2719±12
XV	($C_{29}H_{46}O_6N_2S_2ZnSn$)	2619±12	2219±12	2819±12	2819±12
XVI	($C_{35}H_{34}O_6N_2S_2ZnSn$)	2419±11	2419±11	2919±12	2919±12
Flucanazol (reference)		3019±11	2919±12	4019±12	3919±12

*No activity

Platinum-group fourteen elements

The chemistry of multimetallic systems is an emerging area of material science as documented by the increase in the number of publications [28]. Various metals have been incorporated in all of the topologically different parts of dendritic structures providing new materials which, in some cases have been shown to possess interesting properties in catalysis [29, 30], electrochemistry, photophysics [31] and as molecular sensor for gas. Platinum metal have attracted considerable interest owing to their anticancer activity and biological activity [32]. Sharma et al. synthesized biologically potent tetraazamacrocyclic heterobimetallic complexes of silicon, tin, titanium, zirconium and platinum $[Pt(C_4H_{13}N_3)_2M'_2(R)_4]Cl_2$ (17) by the reactions of monometallic $[Pt(C_4H_{13}N_3)_2]Cl_2$ with organometallic compounds of silicon, tin, titanium and zirconium (**Figure 7**). The complexes were characterized by physicochemical and spectroscopic methods and a square planar geometry has been suggested for the resulting macrocyclic complexes [33].

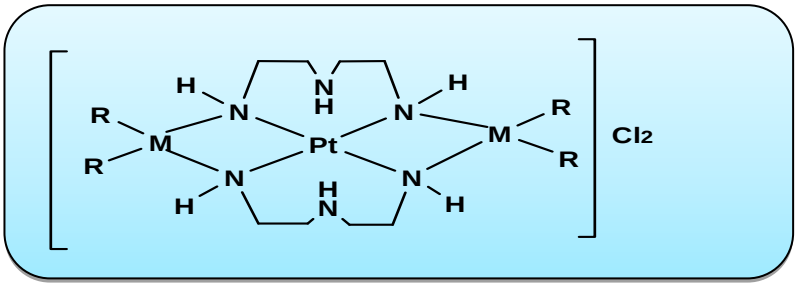

Figure 7 Structure of tetraazamacrocyclic heterobimetallic complex of Platinum.

These complexes show good fungicidal and bactericidal activities against a number of fungi and bacteria (**Tables 5** and **6**).

The results (**Tables 5** and **6**) pointed out that the organotin complexes have greater inhibiting power than the organosilicon complexes. Both of these metal complexes show greater activity than titanium and zirconium complexes. It has been concluded that the chelation as well as the addition of a substrate enhance the activity of these complexes [34].

Table 5 Antibacterial Activity of Mono and Bimetallic Complexes (diameter of inhibitions zone after 30h, mm)

Compounds	*Escherichia coli (-)*		*Staphylococcus aureus (+)*		*Pseudomonas cepacicola (+)*	
	500	**1000**	**500**	**1000**	**500**	**1000**
$[Pt(C_4H_{11}N_3)_2]Cl_2$	2	4	2	3	2	3
$[Pt(C_4H_{11}N_3)_2Sn_2(Ph)_4]Cl_2$	9	12	11	12	11	14
$[Pt(C_4H_{11}N_3)_2Sn_2(Me)_4]Cl_2$	6	9	5	8	5	8
$[Pt(C_4H_{11}N_3)_2Si_2(Ph)_4]Cl_2$	8	10	7	9	7	10
$[Pt(C_4H_{11}N_3)_2Si_2(Me)_4]Cl_2$	5	7	4	6	4	6
$[Pt(C_4H_{11}N_3)_2Ti_2(Cp)_4]Cl_2$	3	4	4	5	4	5
$[Pt(C_4H_{11}N_3)_2Zr_2(Cp)_4]Cl_2$	4	5	5	6	4	4

Table 6 Antibacterial Activity of Mono and Bimetallic Complexes (inhibition after 96h, %)

Compound	*Alternaria alternate*		*Fusarium oxysporum*		*Macrophomina phaseolina*	
	100 Ppm	**200 ppm**	**100 ppm**	**200 Ppm**	**100 ppm**	**200 ppm**
$[Pt(C_4H_{11}N_3)_2]Cl_2$	28	45	30	42	30	35
$[Pt(C_4H_{11}N_3)_2Sn_2(Ph)_4]Cl_2$	68	77	69	83	68	85
$[Pt(C_4H_{11}N_3)_2Sn_2(Me)_4]Cl_2$	52	64	61	68	62	77
$[Pt(C_4H_{11}N_3)_2Si_2(Ph)_4]Cl_2$	59	68	68	73	65	79
$[Pt(C_4H_{11}N_3)_2Si_2(Me)_4]Cl_2$	41	49	50	66	58	71
$[Pt(C_4H_{11}N_3)_2Ti_2(Cp)_4]Cl_2$	32	51	36	48	48	59
$[Pt(C_4H_{11}N_3)_2Zr_2(Cp)_4]Cl_2$	36	48	44	56	54	68

Antitumour Agents

Metal-based pharmaceuticals emerging from interface of inorganic chemistry and biology have witnessed spectacular successes; most notably cisplatin is the archetypal inorganic drug. Although a large number of patients have been cured after cisplatin treatment of cancer, the facts are that the precise mechanism of action remains elusive and that severe side effects develop after administration of the treatment, which has opened up research areas for developing new metal-based anticancer drugs with maximal curative potential and minimal side effects [35] for cancer phenotype (cancers are derived from numerous tissues with new multiple etiologies). Design of these metal-based pharmaceuticals depends on the ligand framework, the choice of metal ion, and its oxidation state [36, 37]. Ligands can significantly alter the biological properties by modifying reactivity or substitution inertness. Tailored, multifunctional ligands introduced into the metal-based medicinal agents limit the adverse effects of metal ion overload, inhibit selected metalloenzymes, and facilitate metal ion re-distribution [38]. The use of metal complexes of ligands has led to the synthesis of heterobimetallic complexes which have been tested extensively to treat a wide range of diseases including cancer.

Copper Complexes

Copper exhibits considerable biochemical action either as an essential trace metal or as a constituent of various exogenously administered compounds in humans. In its former role it is bound to ceruloplasmin, albumin, and other proteins, while in its latter it is bound to ligands of various types forming complexes that interact with biomolecules, mainly proteins and nucleic acids. The multifaceted role of copper in biological systems is demonstrated by several studies. In particular the involvement of copper in human diseases has been described from a medicinal-chemical [39] and a biochemical view [40] focusing on the molecular physiology of Cu transport [41].Much of the current research effort is cited on copper homeostasis [42] and its relation to iron metabolism [43] as well as the role of copper in biological processes related to human physiology and pathology [44, 45]. Current interest in Cu complexes is stemming from their potential use as antimicrobial, antiviral, anti-inflammatory, antitumor agents, enzyme inhibitors, or chemical nucleases. Literature supports that Cu (II) ions specifically bind to the N-7 guanine residue of DNA and cause strand breakage [46, 47]. The kinetic analysis of copper DNA interaction and its site-specific binding in DNA have been well-documented [48, 49]. On the contrary, Sn (IV) complexes prefer to bind to the phosphate backbone of the DNA helix (Sn (IV) ions have a hard Lewis acid nature, neutralize the negative charge of phosphate sugar, and bring conformational changes in DNA) [50, 51]. Thus, bimetallic complexes containing Cu (II) and Sn (IV) ions enhance the chemotherapeutic action many-fold as they provide a dual mode of binding at the molecular target site and also exhibit novelty due to preferential selectivity inside the cells [52, 53]. Arjmand et al. synthesized Novel trinuclear complexes $C_{23}H_{31}N_6O_6CuSn_2Cl_5$ (18), $C_{23}H_{31}N_6O_6CuZr_2Cl_5$ (19), $C_{23}H_{31}N_6O_6ZnSn_2Cl_5$ (20), and $C_{23}H_{31}N_6O_6ZnZr_2Cl_5$ (21) which were characterized by spectroscopic (IR, ^1H, ^{13}C, 2D COSY, and ^{119}Sn NMR, EPR, UV-vis, ESI-MS) and analytical methods (**Figure 8**). In complexes 18-21, the geometry of copper and zinc metal ions were described as square-based pyramidal with L-tryptophan coordinated to copper/zinc via carboxylate group while Sn/Zr was present in the hexacoordinate environment. The interaction of complexes 18 and 19 with calf thymus DNA in tris buffer was studied by electronic absorption titration, luminescence titration, cyclic voltammetry, circular dichroism, and viscometric measurements. The emission quenching of these complexes by $[Fe(CN)_6]^{4-}$ depressed greatly when bound to DNA. Observed changes in the circular dichroic spectra of DNA in presence of complexes 18 and 19 supports the strong binding of these complexes with DNA [54]. The relative specific viscosity of DNA bound to these complexes decreased, indicating that the complexes 18 and 19 bind to DNA via covalent binding. The results reveal that the extent of DNA binding of 18 was greater than that of 19. To evaluate the mechanistic pathway of DNA inhibition, counting experiments and MTT assay were employed to assess the induction of apoptosis by complex 18. Western blot analysis of whole cell lysates and mitochondrial fractions with Bcl-2 and p-53 family proteins and caspase-3 colorimetry assay were also carried out on a human neuroblastoma cell line SY5Y.

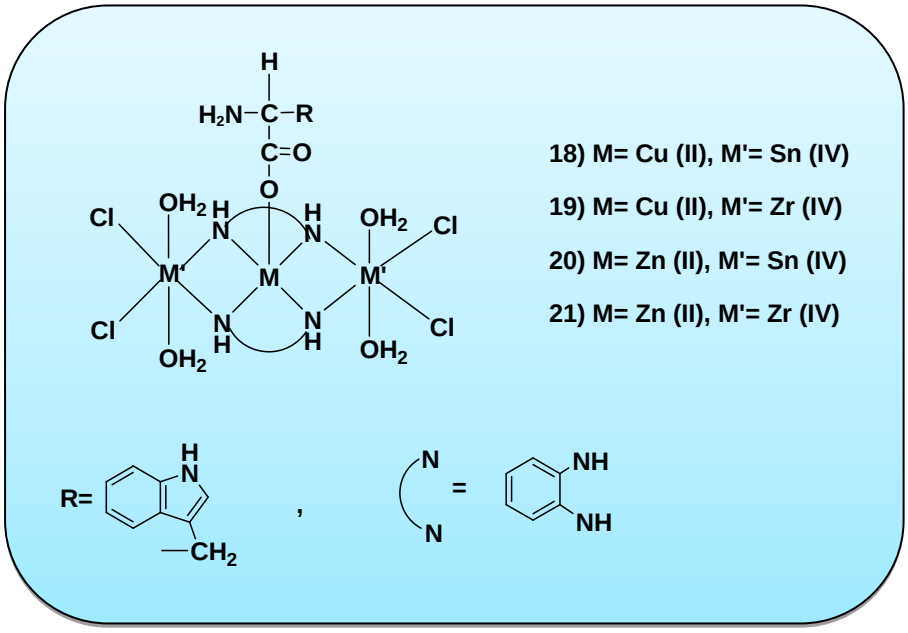

Figure 8 Trinuclear complexes containing L-Tryptophan

The growth inhibitory effect of complex 18 was examined in SY5Y and PC-12 cells using untreated cells as negative controls. In both cases drug treatment in the concentration range between 2 and 8 μM resulted in a dose-dependent inhibition of cell survival.

The design of heteronuclear complexes is based on the concept of combining two functional groups, one of them acting as site specific group, another as scission moiety. Besides this, two homo- or hetero-nuclear metal centers have attracted attention owing to synergistic effect in the process of specific substrate recognition [55]. Guo et al. synthesized monometallic and heteronuclear complexes using bifunctional ligands to explore the binding and cleaving ability of these complexes. It was observed that introduction of another metallic center to Cu (II) complexes resulted in significant enhancement in DNA binding profile underlining the importance of heterobimetallic complexes as compared to monometallic in drug design regime [56-58]. Topoisomerase targeting agents are considered as attractive target for design of cancer chemotherapeutic, because they can cause permanent DNA damage that triggers a series of cellular events, inducing apoptosis and finally causing cell death [59, 60]. Most of topoisomerase inhibitors exhibited several limitations such as poor solubility, dose-limiting toxicity, reversibility of cleavage complex formation, and resistance mechanism developed [61]. Therefore, new anticancer topoisomerase inhibitor chemical entities were designed possessing Cu(II)–Sn(IV) (complex 22) and Ni(II)–Sn(IV) (complex 23) heterobimetallic cores by Tabassum et al. (**Figure 9**).

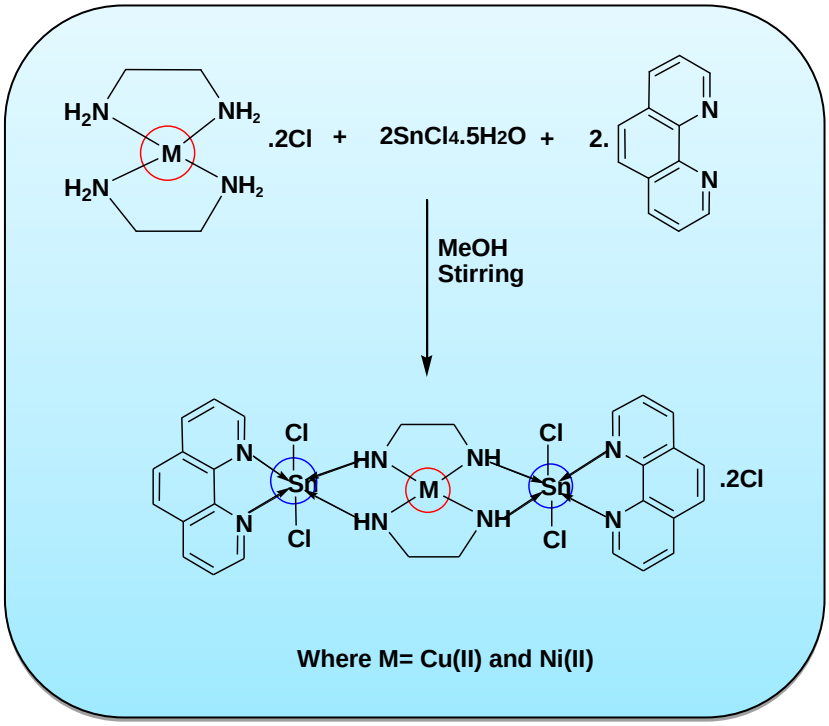

Figure 9 Synthetic route for the heterobimetallic complexes bearing 1,10-phenanthroline and ethylenediamine

The ligand scaffold chosen was common pharmacophoric planar heterocyclic phenanthroline as an element of specific recognition with copper/nickel center metal binding domain-the ethylenediamine unit [62]. This design show novelty as it fulfills all the pre-requirements for efficient robust chemotherapeutic entity:

(i) a well-defined characteristic crescent shape and metal binding domain
(ii) good DNA binding affinity
(iii) specific binding to drug target at molecular level
(iv) efficient DNA cleavage and potent topoisomerase I inhibition.

In vitro anticancer activity of complex 22 has been evaluated in terms of GI_{50}, TGI and LC_{50} (**Table 7**) values against nine different human carcinoma cell lines of different histological origin: 786-O, A498 (kidney), Zr-75-1 (Breast), SiHa (Cervix), A549, Hop-62 (Lung), SW620, HCT15 (Colon), MIAPACA2 (Pancreatic). The Sulforhodamine-B

(SRB) assay was used to assess the cellular proliferation [63]. The result showed high potential of the complex 22 as drug candidate, as expected from the in vitro DNA binding studies and topoisomerase I catalytic inhibition. The complex 22 exhibited very promising antitumor activity (GI_{50} < 10µg/mL) against all these human carcinoma cell lines, indicating that it has the potential to act as efficacious metal-based anticancer drug.

Table 7 Screening data of complex 22 for the anti-tumour activity (in µg/mL)

Human tissue		**Kidney**	**Breast**	**Cervix**	**Lung**	**Colon**	**Lung**	**Colon**	**Kidney**	**Pancrea**
Cell line		786-O	Zr-75-1	SiHa	Hop62	HCT15	A549	SW620	A498	MIAPACA2
	1	<10	<10	<10	<10	<10	<10	<10	<10	<10
GI_{50}	ADR	<10	<10	<10	<10	<10	<10	<10	<10	<10
	1	35.4	<10	14.4	<10	26.6	21.9	<10	11.4	35.7
TGI	ADR	26.5	<10	14.9	10.1	37.0	42.1	17.0	13.9	20.4
	1	79.1	18.7	51.1	24.7	64.5	45.8	32.8	35.0	83.6
LC_{50}	ADR	55.9	22.2	32.6	31.0	66.9	77.8	34.3	35.3	46.8

Where GI_{50}=growth inhibition of 50% calculated from [(Ti-Tz)/(C-Tz)] × 100=50, drug concentration result in a 50% reduction in the net protein increase.
ADR= Adriamycin (taken as positive control compound)
TGI= tumour growth inhibition.
LC_{50}= lethal concentration of 50%

Interactions of DNA with transition metal complexes are important for the design of efficacious drug entities which exhibit different properties than the mainstream protocol drugs viz. cisplatin, etc. which are currently in use [64]. Keeping this in mind, Arjmand et al. synthesized a novel heterobimetallic Cu(II)- Sn(IV) complex (24) bearing bioactive 1,10-phenanthroline pharmacophore ligand scaffold and characterized it by elemental analysis, IR, UV-vis spectroscopy, mass (ESI and FAB) and x-ray crystallography (**Figure 10**). The in vitro DNA binding studies of complex 24 with CT DNA was carried out by various biophysical and molecular docking techniques which revealed that complex 24 binds to DNA through intercalation in the minor groove having AT-rich sequences [65].

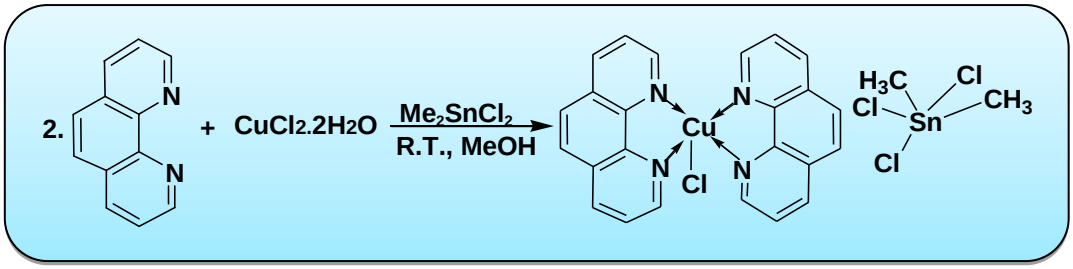

Figure 10 Synthetic route for heterobimetallic Cu (II)-Sn (IV) complex bearing 1,10- phenanthroline

This complex binds supercoiled plasmid pBR322 DNA and displays efficient hydrolytic cleavage as ascertained by gel electrophoretic assays. This could be attributed to its dual binding affinity of metal ions in particular, Sn(IV) which is generally a specific recognition element for hydrolytic cleavage. The hydrolytic cleavage mechanism of the complex is supported by evidence from DNA relegation employing T4 DNA ligase assay and was validated from free radical quenching. Furthermore, complex exhibits high inhibitory effect on Topo I at a very low concentration ~15 µM suggesting that it is an efficient catalytic inhibitor of human Topo I and therefore is a potential anti-tumour drug entity. Once again using copper Arjmand and co-workers synthesized the new chiral trinuclear complex, [bis (aquodiaminotryptophanato) Cu II–Sn_2 IV] chloride (25) by employing a well-designed three-step pathway under

anhydrous conditions (**Figure 11**). Interaction of the complex (25) with calf-thymus DNA was studied by spectrophotometry, cyclic voltammetry and viscosity measurements [66]. Amino acids in combination with ligands such as ethylenediamine, can form stable trinuclear complexes with tin(IV) and copper/ nickel(II). The chiral auxillary as tryptophan incorporated in the metal complexes can generate more selective and active metal center, which is well tuned to adapt a different stereochemistry. The interaction studies of complex (25) with calf-thymus DNA suggest that it is a strong stereoselective inhibitor of DNA as Cu II center preferentially attacks at the N7 position of guanine while Sn IV atom binds to the phosphate backbone of DNA helix. This complex is a promising candidate for cancer chemotherapy.

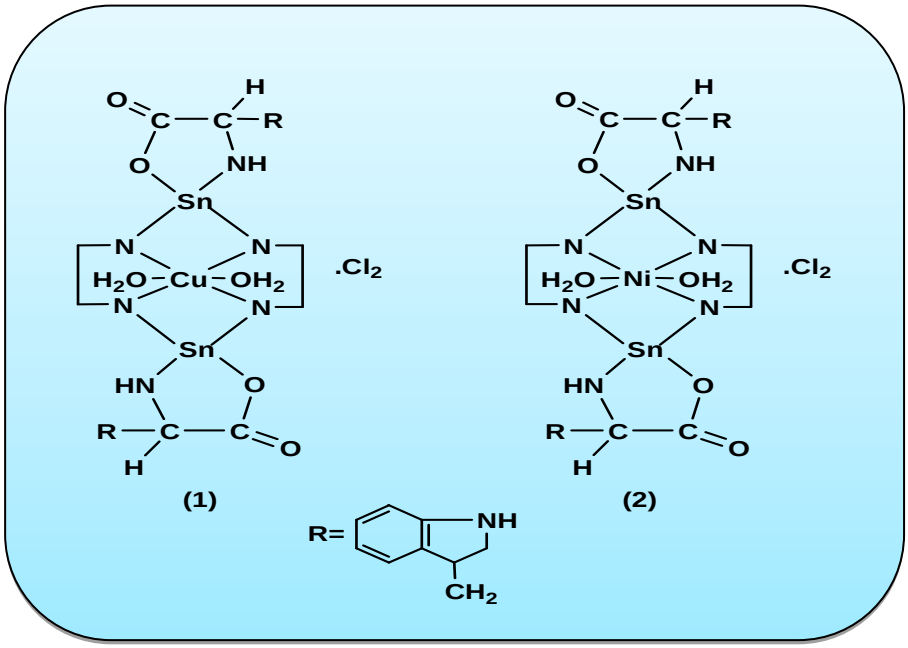

Figure 11 Synthesis of chiral trinuclear complex, [bis (aquodiaminotryptophanato)Cu II–Sn_2 IV] chloride

DNA topoisomerase I and II are established molecular targets of anti-cancer drugs [67-69]. Topoisomerases are crucial for cellular genetic process such as DNA replication, transcription, recombination and chromosome segregation at mitosis [70, 71] and several class of topoisomerase inhibitors have been introduced into cancer clinics as potent anti-cancer drugs [72]. Topo II is closely regulated in normal cells, but tumours maintain high level of topo II, a target for several antitumour agents [73]. Muddassir et al. synthesized new heterobimetallic topoisomerase I and II inhibitors derived from salicylaldimine pharmacophore containing Cu(II)–Sn_2(IV)/Zn(II)–Sn_2(IV) metallic cores which are major and minor groove binders, respectively (**Figure 12**). Insertion of second metal, Sn(IV) (a hard Lewis acid) neutralizes the dinegative charge of phosphate sugar, further tunes/modulates the monometallic complexes to behave as sitespecific oriented cancer chemotherapeutic agents. The unique signature of transition metal ions, Cu(II)/Zn(II) together with Sn(IV) – a non-transition metal ion exhibits dual mode of action in vivo due to its preferential selectivity inside the cells . Cu(II) have distinct preference for covalent mode of binding via N7 of guanine while Zn(II) effectively function to recognize N3 of thymine nucleobase whereas Sn(IV) prefers to bind to oxygen atom of the phosphate sugar backbone of DNA helix [74]. Besides this, copper and zinc complexes have established biological properties; they are the most abundant trace elements present in biological systems and several metalloprotiens contain one or both elements [75]. Since DNA topoisomerase I and II are the ultimate molecular targets of anti-cancer drugs, the interaction studies of the complexes 26 (Cu-Sn_2) and 27 (Zn-Sn_2) were carried out with CT DNA, nucleotides viz, 5'-GMP and 5'-TMP (in comparison to their monometallic complexes and the Schiff base ligand) and inhibitory activity with topoisomerases was examined [76]. Spectroscopic results demonstrate that complex 26 shows high inhibition activity against Topo I at a very low concentration and since such inhibitions are related to DNA binding therefore, they can act as potent antitumour drugs.

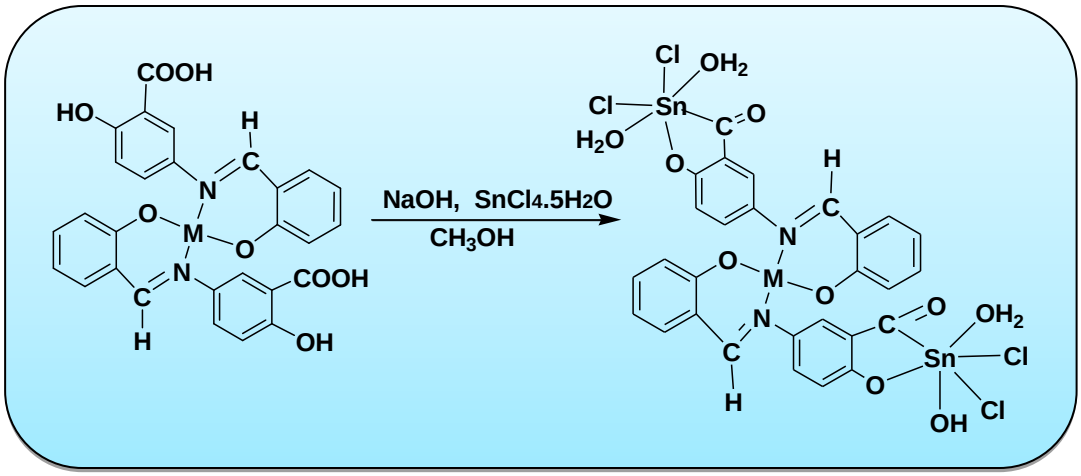

Figure 12 Heterobimetallic topoisomerase I and II inhibitors derived from salicylaldimine pharmacophore containing Cu(II)–Sn_2(IV)/Zn(II)–Sn_2(IV) metallic cores

Ruthenium Complexes

Heterobimetallics is one of the most rapidly developing areas of pharmaceutical research and has attracted much attention by exhibiting promising anti-tumour activity.In the recent years, ruthenium complexes have emerged as the most promising alternatives to platinum-based substances for the development of new metallo-pharmaceuticals due to their favorable properties, such as lower toxicity toward healthy tissues, high cytotoxicity against cancer cells, various oxidation states under physiological conditions, and higher coordination number and ligand exchange kinetics similar to those of platinum complexes [77-79]. Taking into consideration the fact that bimetallic complexes enhance the chemotherapeutic action manyfold, as they provide a dual mode of binding at the target site and exhibit novelty in preferential selectivity inside the cell Khan et al. synthesized the chloro-bridged heterobimetallic complex [80] (η^6-hexamethylbenzene)Ru(dmp)(μ-Cl)$_2$Sn(CH_3)$_2$$Cl_2$ (28) and characterized it by various spectroscopic methods, viz. IR, ^{1}H and ^{13}C NMR, ESI MS and single-crystal X-ray crystallography (**Figure 13**).

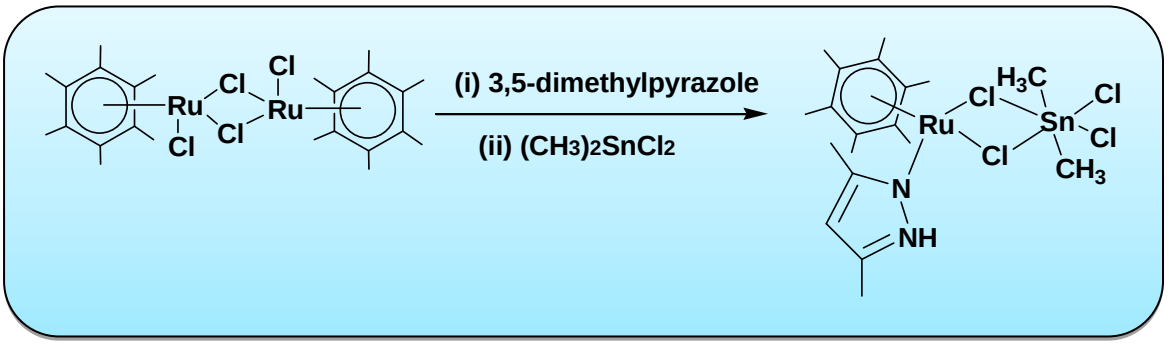

Figure 13 Reaction scheme for the synthesis of the chloro-bridged heterobimetallic complex (η^6- hexamethylbenzene)Ru(dmp)(μ-Cl)$_2$Sn(CH_3)$_2$$Cl_2$

This complex is expected to exhibit a unique dual mode of preferential binding with CT DNA. A red shift can be indicative of coordination of Ru (II) through the N7 position of guanine, whereas Sn (IV) ions (non-transition-metal ion) of the complex exhibit preferential selectivity toward the phosphate group of the DNA backbone, causing contraction and conformational change in the DNA helix and hence resulting in breakage of the secondary structure of the DNA [81].The intrinsic equilibrium DNA-binding constant (K_b) value for the complex is 4.51×10^5 M^{-1}. This higher value of K_b is attributed to the dual mode of interaction due to preferential selectivity of the heterobimetallic core. The cytotoxicity of the complex against HeLa and HepG2 cancer cells was evaluated using the MTT assay and

exhibited significantly good cytotoxicity on both cancer cell lines. The IC_{50} values of the complex were found to be 5.2 and 7.4 μM, as compared to 5.8 and 11.2 μM for the standard cis-$Pt(NH_3)_2Cl_2$ on HeLa and HepG2, respectively. The in vitro DNA binding studies of the complex revealed an electrostatic mode of binding as well as selective binding to the minor groove of DNA. The complex cleaves supercoiled pBR322 DNA through an oxidative (O_2-pathway) cleavage mechanism induced by a reactive oxygen species (ROS). Furthermore, the complex exhibited significant inhibitory effects on human Topo-Iα activity at a very low concentration of 8 μM . The Topo I inhibitory activity is significantly higher than that for some of the classical Topo Iα inhibitors used clinically as antitumor drugs.

Flavonoid Complexes

DNA is generally the primary intracellular target of anticancer drugs, so the interaction between small molecules and DNA can cause DNA damage in cancer cells, blocking the division of cancer cells, and resulting in cell death [82, 83]. Small molecules can interact with DNA through the following three noncovalent modes: intercalation, groove binding, and external static electronic effects [84].The interaction of metal complexes of flavonoids notably quercetin with DNA exhibits biochemical and biological importance, such as anticancer, antiviral, antibacterial, antioxidants, and anti-inflammatory effects. DNA–quercetin interaction has been studied intensively, since these molecules exhibited a high potential to act as chemotherapeutic agents, mainly in cancer chemotherapy. New heterobimetallic quercetin–Cu(II)–Sn_2(IV) and Zn(II)–Sn_2(IV) complexes (29 and 30) were designed and synthesized to act as potential cancer chemotherapeutic agents (**Figure 14**).

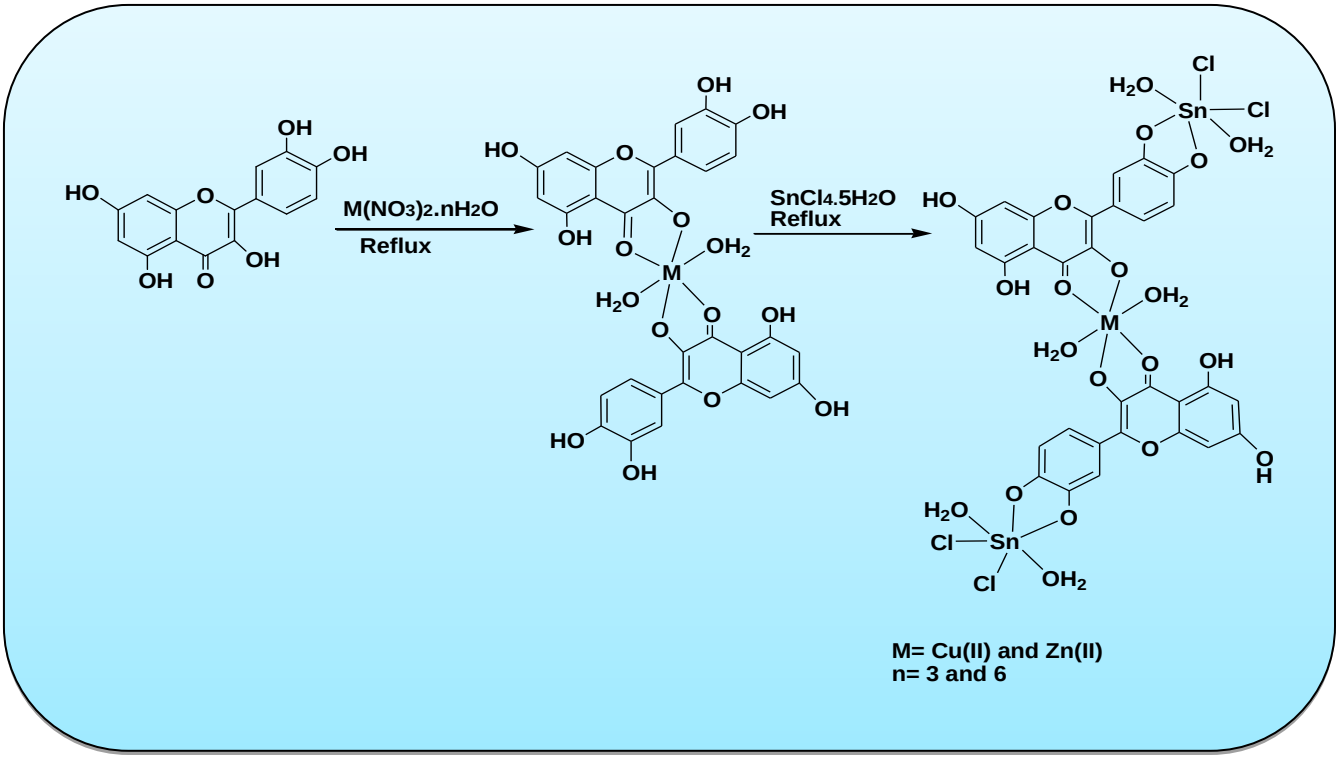

Figure 14 Synthetic route to monometallic and heterobimetallic complexes of Cu and Zn using quercetin (flavonoid)

It has been demonstrated that copper accumulates in tumors due to selective permeability of the cancer cell membrane to copper compounds thereby they can act as "artificial nucleases" for the sequence specific disruption of gene function. While zinc as an essential element plays a vital role in many physiological, and pathological processes. Zinc controls cell proliferation, differentiation, and viability including apoptosis. On the other hand tin complexes show preferential selectivity towards the oxygen atom of the polyanionic structure of DNA, Sn IV ions possess a hard Lewis acid nature, and interact with the phosphate backbone and thus bring about conformational changes in DNA. Thus, heterobimetallic complexes containing Cu II/Zn II and Sn IV ions enhance the chemotherapeutic action many-fold as they provide a dual mode of binding at the molecular target site and also exhibit novelty due to preferential

selectivity inside the cells [85]. The interaction of these complexes with CT DNA by UV-vis was evaluated by UV-vis and fluorescence spectroscopy revealing an electrostatic mode of binding. Quercetin complexes are capable of promoting DNA cleavage involving both single and double strand breaks [86]. Complex 29 cleaved pBR322 DNA via an oxidative mechanism while complex 30 followed a hydrolytic pathway, accessible to the minor groove of the DNA double helix in accordance with molecular docking studies with the DNA duplex of sequence $d(CGCGAATTCGCG)_2$ dodecamer demonstrating that the complex was stabilized by additional electrostatic and hydrogen bonding interactions with the DNA.

The cytotoxic activity of complexes was evaluated in terms of GI_{50}, TGI and LC_{50} (**Table 8**) values against different human carcinoma cell lines of different histological origin: U373MG (CNS), PC3 (Prostate), Hop62 (Lung), HL60 (Leukemia), HCT15 (Colon), A2780 (Ovarian) and HeLa (Cervix).

Table 8 Screening data of complexes 29 and 30 for the in vitro anti-tumour activity (in μM)

Human tissue		**CNS**	**Prostrate**	**Lung**	**Leukemia**	**Colon**	**Ovarian**	**Cervix**
		U373MG	**PC3**	**HOP62**	**HL60**	**HCT15**	**A2780**	**HeLa**
GI_{50}	1	<8.7	<8.7	<8.7	<8.7	<8.7	>69.6	<8.7
	2	42.5	40.0	36.5	31.9	42.8	41.1	7.2
	ADR	<17.2	<17.2	<17.2	<17.2	<17.2	56.0	<17.2
TGI	1	9.8	14.2	18.6	55.3	11.4	<137.9	<8.7
	2	>69.4	>69.4	>69.4	>69.4	>69.4	>69.4	44.4
	ADR	48.7	18.1	65.6	107.4	56.3	134.3	<17.2
LC_{50}	1	42.8	49.6	51.5	>69.6	45.8	>69.6	36.4
	2	>69.4	>69.4	>69.4	>69.4	>69.4	>69.4	>69.4
	ADR	116.7	85.68	>137.9	>137.9	>137.9	>137.9	>137.9

Where: GI_{50}=growth inhibition of 50% calculated from[(Ti-Tz)/(C-Tz)]X 100=50, drug concentration result in a 50% reduction in the net protein increase.
ADR= Adriamycin (taken as positive control compound)
TGI = tumour growth inhibition.
LC_{50} = lethal concentration of 50%

The in vitro anti-tumor screening was evaluated by applying micro culture Sulforhodamine B test (SRB)[50] and results revealed that complex 29 is more cytotoxic than that of the corresponding complex 30 against various human cancer cell lines, with a potency similar to that of the anticancer drug Adriamycin. These results showed the high potential of complex 29 to act as a drug candidate, as expected from the in vitro DNA binding studies and topoisomerase I catalytic inhibition. Among both the complexes, 29 exhibited very promising antitumor activity ($GI50 < 10\ \mu g\ ml^{-1}$) against all these human carcinoma cell lines, indicating that it has the potential to act as an efficacious metal-based anticancer drug.

Gold Complexes

The clinical effectiveness of cisplatin and - to some extent- of its analogues, is often limited by severe toxic side-effects, due to the rather poor ability of Pt drugs to distinguish between malignant and normal cells, as well as to the frequent occurrence of intrinsic and acquired cancer resistance to platinum [87, 88]. Such severe drawbacks have spurred researchers to look for alternatives, both in the frame of platinum-based compounds [89, 90] and in that of other transition metal derivatives [91, 92]. Nevertheless, in spite of the variety of molecular mechanisms displayed by the different classes of platinum complexes, almost invariantly nuclear DNA turned out to be the main target for most of them with the consequence that resistance processes are often activated after prolonged exposure to Pt drugs. For

the above mentioned reasons, in order to broaden the spectrum of activity, many researchers focused attention on the potential of anticancer drugs containing non-platinum metal centers. Among them, ruthenium [93] and gold-based [94] drugs were shown to be a promising alternative or, at least, to be complementary to platinum(II) anticancer drugs. A new heterodimetallic combination based on Pt(II) and Au(I) was developed by Cinellu and co-workers via exploiting the great versatility of 2-(2′-pyridyl)-benzimidazole (pbiH) as a potential bridging ligand. A novel platinum (II) organometallic complex, [Pt(pbi)(Me)(DMSO)] (32), bearing the 2-(2′-pyridyl)-benzimidazole (pbiH) ligand, was synthesized and fully characterized. Interestingly, the reaction of this organometallic platinum(II) complex with two distinct gold(I) phosphane compounds afforded the corresponding heterobimetallic derivatives (32a and 32b) with the pbi ligand bridging the two metal centers [95]. The antiproliferative properties *in vitro* of [Pt(pbi)(Me)(DMSO)] and its gold(I) derivatives as well as those of the known coordination platinum(II) and palladium(II) complexes with the same ligand, of general formula [MCl_2(pbiH)] (31), were comparatively evaluated against A2780 cancer cells, either sensitive or resistant to cisplatin. A superior biological activity of the organometallic compound clearly emerged compared to the corresponding platinum (II) complex; the antiproliferative effects are further enhanced upon attaching the gold (I) triphenylphosphine moiety to the organometallic Pt compound. Remarkably, these novel metal species are able to overcome nearly completely resistance to cisplatin (**Figure 15**).

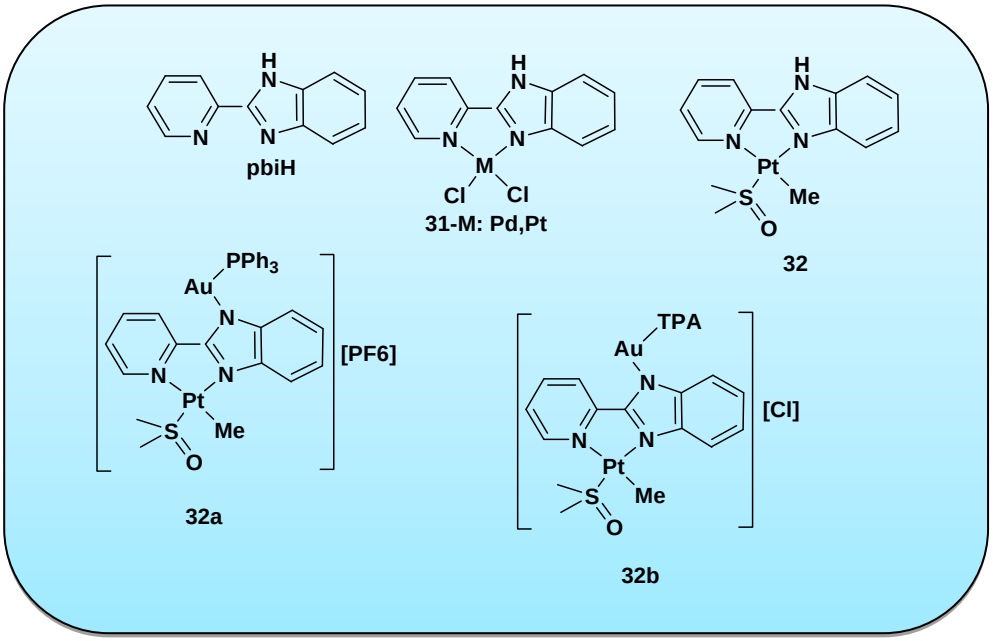

Figure 15 Organometallic Platinum (II) complex and its Gold (I) heterobimetallic derivatives

Since the discovery of transition-metal complexes with N heterocycliccarbenes (NHCs) by Wanzlick and Öfele in 1968 [96] NHCs have become established ligands in organometallic chemistry and homogeneous catalysis. NHCs can be easily modified by attaching functional groups at their nitrogen atoms that can act as additional donor ligands. NHC ligands with nitrogen, oxygen, phosphorus, or sulfur as donor atoms have been described. Such functionalized ligands or polycarbene systems give access to bimetallic complexes. In contrast to homobimetallic complexes, only a limited number of heterobimetallic transition-metal complexes with NHC ligands have been reported. Three heterobimetallic gold(I)−ruthenium(II) complexes containing heteroditopic bipyridine−N-heterocyclic carbene (NHC) ligands were synthesized by Boselli et al. , fully characterized by spectroscopic methods and by single-crystal X ray diffraction (**Figure 16**).

These mixed-metal complexes have been designed for two distinguished properties: photophysical properties concerning the ruthenium part and biological activities concerning the gold unit [97]. In addition, the in vitro cytotoxic, antileishmanial, and antimalarial activities of these new heterobimetallic complexes were assessed. These compounds presented herein except for the silver complexes were tested in vitro against Leishmania infantum

promastigotes, Plasmodium falciparum FcB1-Colombia strain, and the human hepatocellular carcinoma (Hep3B) cell line. The tested compounds show moderate activities or absence of activity (**Table 9**).

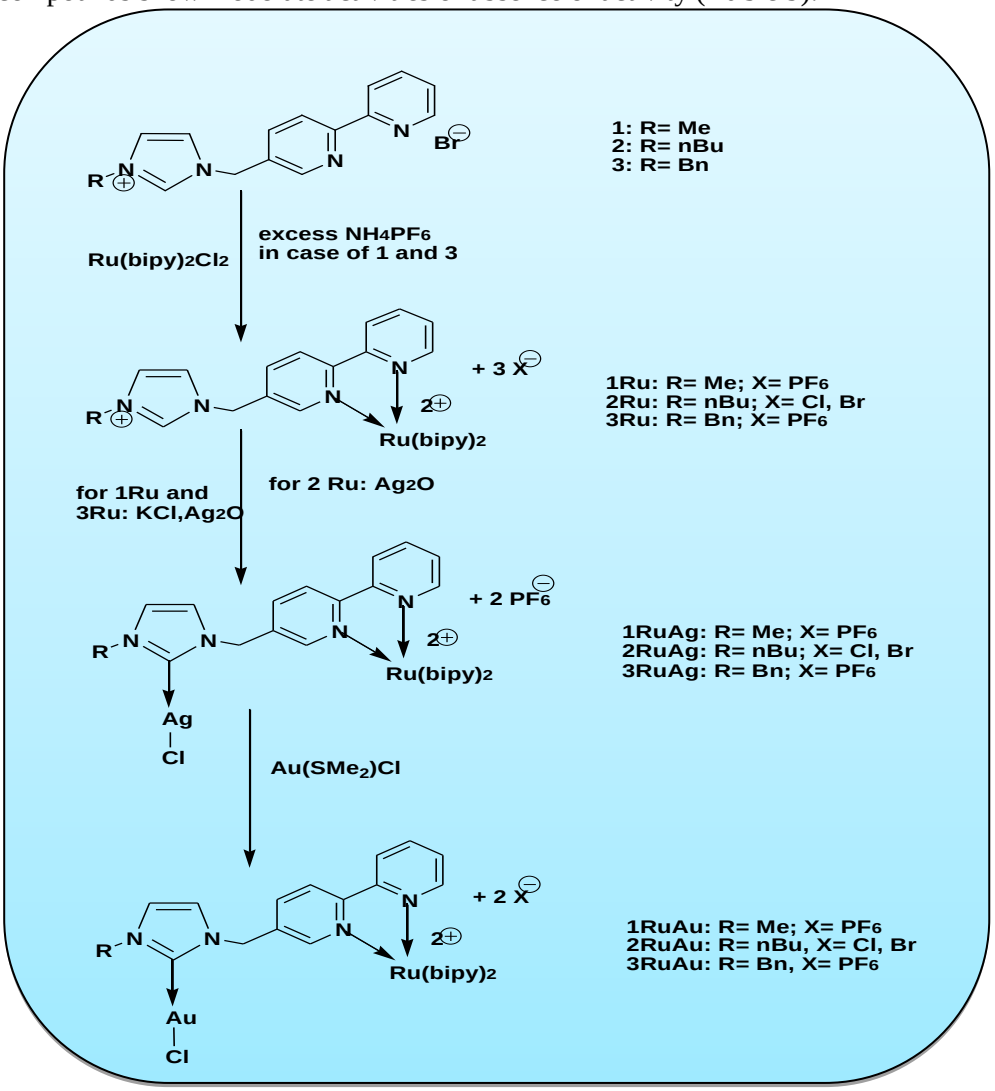

Figure 16 Synthetic route for heterobimetallic complexes of transition metals with NHC ligand

Table 9 Antileishmanial, antiplasmodial and cytotoxic activities (IC_{50}, µM) of proligands 1-3,ruthenium complexes 1Ru to 3Ru and heterobimetallic Ru-Au complexes 1RuAu to 3RuAu

Compound	*L.infantum* (promastigotes)	*P. falciparum*	Hep 3B
1	>50	>50	-
2	>50	17.6 (4.0)	-
3	>50	39.3 (3.5)	-
1Ru	>50	>50	>100
2Ru	>50	>50	>100
3Ru	>50	>50	>100
1RuAu	>50	25.5 (5.6)	30.4
2RuAu	>25	16.1 (2.2)	17.1
3RuAu	>50	15.8 (4.1)	18.9

Reference	0.01 (Amphotericin B)	0.19 (0.02) (Chloroquin)	7.2 (Sorafenib)

Conclusion: Changing Perspectives, Overcoming Barriers

With the advancement in the field of inorganic chemistry the role of heterobimetallic complexes as therapeutics is becoming increasingly important. As illustrated by the examples summarized in this review, much progress has been made in the area of heterobimetallic complexes. Rapid advances in the field of bimetallic complexes are increasingly making it possible to synthesize heterobimetallics that serve valuable roles as therapeutic agents and thus offers hope in the fight against scourge of deadly disease that have continued to ravage mankind. These complexes offer a great diversity in their action and are thus being used as antitumour, antibacterial and antifungal agents. Development of heterobimetallic complexes is not an easy task as considerable efforts are required to get a compound of interest. Besides all these obstacles, heterobimetallic complexes are largely synthesized and thus make a large contribution to medicinal therapeutics in a way that was, unimaginable in few years back. The future of this field lies in gaining a better understanding of the fundamental transformations occurring at heterobimetallic centers and assessing the independent roles of each metal and metal–metal bond in reactivity.

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References

[1] Cohen SM, Curr. Opin. Chem. Biol., 2007, 11, 115.
[2] Thompson KH, Orvig C, Dalton Trans., 2006, 29, 761.
[3] Thomas CM, Comment Inorg. Chem., 2011, 32, 14.
[4] Rakkiyasamy M, Kalimuthu K, Rangasamy S, J. Chem. Bio. Phy. Sci. Sec. A, 2013, 3, 16.
[5] Copper BG, Napoline JW, Thomas CM, Catalysis reviews, 2012, 54, 1.
[6] Puckett CA, Barton JK, Biochemistry, 2008, 47, 11711.
[7] Haas KL, Franz KJ, Chem. Rev., 2009, 109, 4921.
[8] Willem R, Dalil H, Brockaert P, Biesemans M, Ghys L, Nooter K, Ribot F, Gielen M, Main Group Met Chem., 1997, 20, 535.
[9] Kemmer M, Gielen M, Biesemans M, Wilem R, Met Based Drugs, 1998, 5, 189.
[10] Malhotra R, Mehta J, Bala K, Sharma AK, Indian J. Chem., 2008, 47,58.
[11] Hadjikakou SK, Hadjiliadis N, Coord. Chem. Rev., 2009, 253, 235.
[12] Hadjikakou SK, Ozturk I I, Xanthopoulou MN, Zachariadis PC, J. Inorg. Biochem., 2008, 102, 1007.
[13] Islami-Moghaddam M, Mansouri-Torshizi H, Divsalar A, Saboury AA, J. Iranian Chem. Soc., 2009, 6, 552.
[14] Hussain S, Ali S, Shahzadi S, Shahid M, Cogent Chem., 2015, 1, 1.
[15] Mohan M, Gupta NS, Gupta MP, Kumar A, Kumar M, Jha NK, Inorg.Chim. Acta., 1988, 25, 152.
[16] Maiti A, Ghosh S, J. Inorg. Biochem., 1989, 36, 131.
[17] Singh VP, A. Singh A, Toxicol. Enviorn. Chem., 2008, 90, 565.
[18] Nagar R, J. Inorg. Biochem., 1990, 40, 349.
[19] Singh VP, Gupta P, J. Coord. Chem., 2006, 59, 1483.
[20] Liu ZC, Wang BD, Li B, Wang Q, Yang ZY, Li TR, Li Y, Eur. J. Med. Chem., 2010, 45, 5353.
[21] Dimiza F, Papadopoulos AN, Tangoulis V, Psycharis V, Raptopoulou CP, Kessissoglou DP, Psomas G, Dalton Trans., 2010, 39, 4517.
[22] Tabassum S, Zaki M, Arjmand F, Ahmad I, J. Photochem. Photobio. B: Biology, 2012,114, 108.
[23] Lakshmia PVA, Reddy PS, Raju VJ, Spectrochim. Acta A, 2009, 74, 52.
[24] Ji-Chun C, Yan-Lng Q, Long-Hua D, Han-Dong Y, Chin. J. Stru. Chem., 2010, 29, 1784.
[25] Jamil K, Wajid R, Bakhtiar M, Danish M, J. Iran. Chem. Soc., 2010, 7, 495.
[26] Iram S, Ali S, Shahzadi S, Shahid M, Russ. J. Gen. Chem., 2013, 83, 2453.
[27] Joseyphus RS, Nair M, Mycobiol., 2008, 36, 93.
[28] Hearshaw MA, Moss JR, Chem. Commun., 1997, 1.
[29] Brunner H, Janura M, Stefaniak S, Synthesis, 1998, 12, 1742.

[30] Reetz MT, Lohmer G, Schwick R, Angew, Chem. Int. Ed. Engl., 1997, 36, 1526.
[31] Valerio C, Fillant JL, Ruiz J, Guittard J, Blais JC , Astruc D, J. Am. Chem. Soc., 1997, 119, 2588.
[32] Dunbar KR, Matonic JH, Saharan VP, J. Am. Chem. Soc., 1994, 116, 2201
[33] Sharma K, Fahmi N, Singh RV, Main Group Met. Chem., 2002, 25, 727.
[34] Moore EC, Zeleck MS, Agrawal KC, Sartorelli AC, Biochemistry, 1970, 9, 4492.
[35] Reedijk J, Chem. Commun., 1996, 32 ,801.
[36] Thompson KH, Orvig C, Science, 2003, 300, 936.
[37] Reedijk J, Proc. Natl. Acad. Sci. U.S.A, 2003, 7, 3611.
[38] Storr T, Thompson KH, Orvig C, Chem. Sci. Rev., 2006, 35, 534.
[39] Brewer GJ, J. Am. Coll. Nutr., 2009, 28, 238.
[40] Daniel KG, Gupta P, Harbach RH, Guida WC, Dou QP, Biochem. Pharmacol., 2004, 67, 1139.
[41] Puig S, Thiele DJ, Curr. Opin. Chem. Biol., 2002, 6, 171
[42] Balamurugan K, Schaffner W, Biochimica et Biophysica Acta, 2006, 1763, 737.
[43] Arredondo M, Nunez MT, Mol. Aspects Med., 2005, 26, 313.
[44] Uriu-Adams JY, Keen CL, Mol. Aspects Med., 2005, 26, 268.
[45] Crisponi G, Nurchi VM, Fanni D, Gerosa C, Nemolato S, Faa G, Coord. Chem. Rev., 2010, 254, 876.
[46] Ito T, Thyagarajan S, Karlin KD, Rokita SE, Chem. Comm., 2005, 38 , 4812.
[47] Chikira M, Tomizawa Y, Sugizaki T, Sugawara N, Yamazaki T, Sasano A, Shindo H, Palaniandavar M, Antholine WE, Inorg. Biochem., 2002, 89, 163.
[48] Zhang QQ, Zhang F, Wang WG, Wang XL , J. Inorg. Biochem., 2006, 100, 1344.
[49] Chakravarty AR, Reddy PAN, Santra B, Thomas AM, Proc. Indian Acad. Sci., 2002, 114, 391.
[50] Zelder FH, Mokhir AA, Kramer R, Inorg. Chem., 2003, 42, 8618.
[51] Hoti N, Ma J, Tabassum S, Wang Y, Wu M, J. Biochem., 2003, 134, 521.
[52] Hoti N, Zhu D, Song Z, Wu Z, Tabassum S, Wu M, J. Pharmacol. Exp. Ther., 2004, 311, 22.
[53] Chauhan M, Arjmand F, Transition Met. Chem., 2005, 30, 481.
[54] Chauhan M, Banerjee K, Arjmand F, Inorg. Chem., 2007, 46, 3072.
[55] deHoog P, Pitie M, Amadei G, Gamez P, Meunier B, Kiss R, Reedijk J, J. Biol. Inorg. Chem., 2008, 13, 575.
[56] Chen J, Wang X, Shao Y, Zhu Y, Zhu J, Li Y, Xu Q, Guo Z, Inorg. Chem., 2007, 46, 3306.
[57] Tu C, Shao Y, Gan N, Xu Q, Guao Z, Inorg. Chem., 2004, 43, 4761.
[58] Dang X, Wang X, Lin M, Sun H, Yang X, Guo Z, Inorg. Chem., 2010, 49, 2541.
[59] Liu LF, Annu. Rev. Biochem., 1989, 58, 351.
[60] Denny WA, Expert Opin. Invest. Drugs, 1989, 6, 351.
[61] Beretta GL, Perego P, Zunino F, Curr. Med. Chem., 2006, 13, 3291
[62] Tabassum S, Afzal M, Arjmand F, J. Photochem. Photobiol. B: Biology, 2012, 115, 63.
[63] Lammers T, Peschke P, Ehemann V, Debus J, Slobodin B, Lavi S, Huber P, Mol Cancer, 2007, 6, 65.
[64] Rosenberg B, VanCamp L, Trosko JE, Mansour VH, Nature, 1969, 222, 385.
[65] Arjmand F, Parveen S, Afzal M, Toupet L, Hadda TB, Eur. J. Med. Chem., 2012, 49,141.
[66] Chauhan M, Arjmand F, Transit Metal Chem., 2005, 30, 481.
[67] McClendon AK, Osheroff N, Mutat. Res., 2007, 623 , 83.
[68] Nitiss JL, Nat. Rev. Cancer, 2009, 9, 338.
[69] Gao F, Chao H, Zhou F, Chen X, Wei YF, Ji LN, J. Inorg. Biochem., 2008, 102, 1050.
[70] Pommier Y, Pourquier P, Fan Y, Strumberg D, Biochim. Biophys. Acta, 1998, 1400, 83.
[71] Champoux JJ, Annu. Rev. Biochem., 2001, 70, 369.
[72] Denny WA, Expert Opin. Emerg. Drugs, 2004, 9, 105.
[73] Larsen AK, Escargueil AE, Skladanowski A, Prog. Cell Cycle Res., 2003, 5, 295.
[74] Zelder FH, Mokhir AA, Kramer R, Inorg. Chem., 2003, 42, 8618.
[75] Silvestri A, Barone G, Ruisi G, Anselmo D, Riela S, Liveri VT, J. Inorg. Biochem.,2007, 101, 841.
[76] Arjmand F, Muddassir M, J. Photochem. Photobiol. B: Biology, 2010, 101, 37.
[77] Kisova A, Zerzankova L, Habtemariam A, Sadler PJ, Brabec V, Kasparkova J, Mol. Pharm., 2011, 8, 949.
[78] Xu L, Zhang D, Deng M, Zhang M, Zhou X, Chem. Commun., 2010, 46, 743.
[79] Bruijnincx PC, Sadler PJ, Curr. Opin. Chem. Biol., 2008, 12, 197.
[80] Khan RA, Asim A, Kakkar R, Gupta D, Bagchi V, Arjmand F, Tabassum S, Organometallics, 2013, 32, 2546.

[81] Pellerito L, Nagy L, Coord. Chem. Rev., 2002, 224, 111.
[82] Zuber G, Quada JC, Hecht SM, J. Am. Chem. Soc., 1998, 120, 9368.
[83] Hecht SM, J. Nat. Prod., 2000, 63, 158.
[84] Kalaivani P, Prabhakaran R, Dallemer F, Poornima P, Vaishnavi E, Ramachandran E, Padma VV, Renganathan R, Natarajan K, Metallomics , 2012, 4, 101.
[85] Middleton E, Chithan K, Theoharides TC, Pharmacol. Rev., 2000, 52, 673.
[86] Tabassum S, Zaki M, Afzal M, Arjmand F, Dalton Trans., 2013, 42, 10029.
[87] Rabik CA, Dolan ME, Cancer Treat. Rev., 2007, 33, 9.
[88] Kelland L, Nat. Rev. Cancer, 2007, 7, 573.
[89] Zhang CX, Lippard SJ, Curr. Opin. Chem. *Biol*., 2003, 7, 481.
[90] Wheate NJ, Walker S, Craig GE, Oun R, Dalton Trans., 2010, 39, 8113.
[91] Barry NPE, Sadler PJ, Chem. Commun., 2013, 49, 5106.
[92] Muhammad N, Guo Z, Curr. Opin. Chem. Biol., 2014, 19, 144.
[93] Suss-Fink G, Dalton Trans., 2010, 39, 1673.
[94] Bertrand B, Casini A, Dalton Trans., 2014, 43, 4209.
[95] Serratrice M, Maiore L, Zucca A, Stoccoro S, Landini I, Mini E, Massai L, Ferraro G, Merlino A, Messori L, Cinellu MA, Dalton Trans., DOI:10.1039/c5dt02714d, 2015.
[96] Wanzlick HW, Schonherr HJ, Angew. Chem. Int. Ed., 1968, 80,154.
[97] Boselli L, Carraz M, Mazeres S, Paloque L, Gonzalez G, Vical FB, Valentin A, Hemmert C, Gornitzka H, Organometallics, 2015, 34, 1046.

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