

UNIVERSITI PUTRA MALAYSIA

SYNTHESIS, CHARACTERIZATION AND APPLICATIONS OF MIXEDLIGAND COPPER(II) COMPLEXES CONTAINING SACCHARIN

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By

NUR SHUHADA MOHD MOKHTARUDDIN

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Master of Science

January 2016

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Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Master of Science

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By

NUR SHUHADA MOHD MOKHTARUDDIN

January 2016

Chairman: Thahira Begum, PhD Faculty: Science

Eighteen tridentate Schiff bases derived from thiosemicarbazide were synthesized using various aldehydes and ketones via condensation reaction. Eighteen new mixedligand metal complexes were synthesized by reacting copper saccharinate with the appropriate Schiff bases in water-ethanol mixtures and have been characterized by elemental analysis and conductance, magnetic susceptibility, FTIR and electronic spectroscopic measurements. The complexes formed with general formula $[Cu(sac)(NNS)]/[Cu(sac)(NNS)(H_2O)]$ or $[Cu(sac)(ONS)]/[Cu(sac)(ONS)(H_2O)]$ where NNS and ONS are tridentate ligands. Magnetic and spectral evidence support a four or five-coordinate geometry for the complexes in which the Schiff bases coordinate to the Cu(II) ion as a uninegative charged tridentate ligand through the pyridine nitrogen or phenoxide oxygen atom, azomethine nitrogen atom and thiolate sulphur atom. The saccharinate anion coordinates as a unidentate N-donor ligand. The fifth coordination positions are occupied by the oxygen atom of the aqua ligand. The molar conductance results indicate that the metal complexes were non-electrolytes in DMSO solution. The cytotoxic activities of the complexes and the Schiff bases were evaluated against two breast cancer cell lines, MCF-7 (Estrogen Receptor Positive Human Breast Carcinoma Cells) and MDA-MB-231 (Estrogen Receptor Negative Human Breast Carcinoma Cells). Most of the complexes showed a higher potential compared than their ligands towards both cancer cell lines. The copper complexes were also deposited into copper oxide thin films by using Aerosol-Assisted Chemical Vapour Deposition technique and characterized by XRD and FESEM. The photocurrent activity of the copper oxide thin films was carried out but showed negative results.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk Ijazah Master Sains

SINTESIS, PENCIRIAN DAN APLIKASI-APLIKASI BAGI KOMPLEKS KUPRUM(II) BERLIGAN CAMPURAN YANG MENGANDUNGI SAKARIN

Oleh

NUR SHUHADA MOHD MOKHTARUDDIN

Januari 2016

Pengerusi: Thahira Begum, PhD Fakulti: Sains

Lapan belas bes Schiff tridentat yang diterbitkan daripada tiosemikarbazid telah disintesis menggunakan pelbagai aldehid dan keton melalui tindak balas kondensasi. Lapan belas kompleks logam bercampur ligan yang baru telah disintesis daripada kuprum sakarinat bersama bes Schiff yang sesuai dalam pelarut campuran air-etanol dan telah dicirikan melalui analisis unsur dan konduktiviti, kerentanan magnetik, pengukuran spektroskopi eletronik dan inframerah. Kompleks yang terhasil dengan formula [Cu(sac)(NNS)]/[Cu(sac)(NNS)(H₂O)] am atau [Cu(sac)(ONS)]/[Cu(sac)(ONS)(H₂O)] di mana NNS dan ONS adalah ligan tridentat. Nilai kerentanan magnet dan spektra menyokong geometri kebanyakan kompleks berkoordinatan empat atau lima di mana bes Schiff berkoordinat kepada ion kuprum(II) dan berkelakuan sebagai cas uninegatif ligan tridentat melalui atom nitrogen piridina atau oksigen fenoksida, atom nitrogen azometin dan atom sulfur tiolat. Anion sakarinat berkoordinat sebagai ligan penderma N-unidentat. Kedudukan koordinat yang kelima pula diisi oleh atom oksigen dari molekul air. Nilai konduktiviti menunjukkan kesemua kompleks logam adalah bukan elektrolit di dalam larutan DMSO. Aktiviti sitotoksik kompleks dan bes Schiff telah dikaji terhadap dua jenis sel kanser, MCF-7 (sel kanser payudara dengan reseptor estrogen positif) dan MDA-MB-231 (sel kanser payudara dengan reseptor estrogen negatif). Kebanyakan kompleks menunjukkan potensi yang tinggi terhadap kedua sel kanser berbanding dengan ligan mereka. Kuprum kompleks juga telah didepositkan kepada filem nipis oksida kuprum dengan menggunakan teknik pemendapan wap kimia dengan bantuan aerosol dan telah dicirikan dengan XRD dan FESEM. Aktiviti arusfoto daripada filem nipis kuprum oksida telah dijalankan tetapi menunjukkan keputusan yang negatif.

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LIST OF ABBREVIATIONS

AACVD	Aerosol-Assisted Chemical Vapour Deposition
B.M	Bohr Magneton
CHNS	Carbon, Hydrogen, Nitrogen & Sulphur
DMSO	Dimethylsulphoxide
EToVa	2-hydroxy-3-methoxybenzaldenyde or ortho-vanilin
	Schiff base of 4-ethyl-3-thiosemicarbazide
ETSali	Salicylaldehyde Schiff base of 4-ethyl-3- thiosemicarbazide
ET2AP	2-acetylpyridine Schiff base of 4-ethyl-3-
	thiosemicarbazide
ET2Py	Pyridine-2-aldehyde Schiff base of 4-ethyl-3-
	thiosemicarbazide
ET24D	2,4-dihydroxybenzaldehyde Schiff base of 4-ethyl-3-
	thiosemicarbazide
ET3MP	3-methylpyridine-2-aldehyde Schiff base of 4-ethyl-3-
	thiosemicarbazide
FESEM	Field Emission Scanning Electron Microscopy
FT-IR	Fourier-Transform Infrared
ICP-OES	Inductively Coupled Plasma-Optical Emission
	Spectroscopy
IC ₅₀	Inhibitory concentration at 50%
LMCT	Ligand to metal charge transfer
MCF-7	Human breast carcinoma cells with positive estrogen receptor
MDA-MB-231	Human breast carcinoma cells with negative estrogen
	receptor
MLCT	Metal to ligand charge transfer
MToVa	2-hydroxy-3-methoxybenzaldenyde or ortho-vanilin
	Schiff base of 4-methyl-3-thiosemicarbazide
MTSali	Salicylaldehyde Schiff base of 4-methyl-3-
WIIGun	thiosemicarbazide
MT2AP	2-acetylpyridine Schiff base of 4-methyl-3-
WI ZAI	thiosemicarbazide
MT2Dy	
MT2Py	Pyridine-2-aldehyde Schiff base of 4-methyl-3- thiosemicarbazide
MT24D	2,4-dihydroxybenzaldehyde Schiff base of 4-methyl-3-
MT24D	thiosemicarbazide
MT3MP	3-methylpyridine-2-aldehyde Schiff base of 4-methyl-
	3-thiosemicarbazide
NMR	Nuclear Magnetic Resonance
NNS	Nitrogen-Nitrogen-Sulphur
ONS	Oxygen-Nitrogen-Sulphur
PToVa	2-hydroxy-3-methoxybenzaldenyde or ortho-vanilin
1104a	Schiff base of 4-phenyl-3-thiosemicarbazide
PTSali	Salicylaldehyde Schiff base of 4-phenyl-3-
1 1 9411	thiosemicarbazide
PT2AP	2-acetylpyridine Schiff base of 4-phenyl-3-
1 1 271	thiosemicarbazide

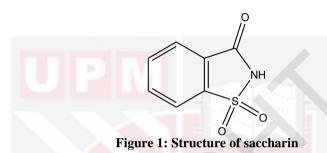
PT2Py	Pyridine-2-aldehyde Schiff base of 4-phenyl-3-
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PT24D	2,4-dihydroxybenzaldehyde Schiff base of 4-phenyl-3-
	thiosemicarbazide
PT3MP	3-methylpyridine-2-aldehyde Schiff base of 4-phenyl-
	3-thiosemicarbazide
Sac	Saccharin anion
SXRD	Single Crystal X-ray Diffraction
UV/Vis	Ultraviolet/Visible Spectroscopy
XRD	X-Ray Diffraction
4E3T	4-ethyl-3-thiosemicarbazide
4M3T	4-methyl-3-thiosemicarbazide
4P3T	4-phenyl-3-thiosemicarbazide
[Cu(sac)(EToVa)]	Copper(II) saccharinate complex of EToVa
[Cu(sac)(ETSali)]	Copper(II) saccharinate complex of ETSali
[Cu(sac)(ET2AP)]	Copper(II) saccharinate complex of ET2AP
[Cu(sac)(ET2Py)]	Copper(II) saccharinate complex of ET2Py
$[Cu(sac)(ET24D)(H_2O)]$	Copper(II) saccharinate complex of ET24D
[Cu(sac)(ET3MP)]	Copper(II) saccharinate complex of ET3MP
[Cu(sac)(MToVa)]	Copper(II) saccharinate complex of MToVa
[Cu(sac)(MTSali)]	Copper(II) saccharinate complex of MTSali
[Cu(sac)(MT2AP)]	Copper(II) saccharinate complex of MT2AP
[Cu(sac)(MT2Py)]	Copper(II) saccharinate complex of MT2Py
$[Cu(sac)(MT24D)(H_2O)]$	Copper(II) saccharinate complex of MT24D
[Cu(sac)(MT3MP)]	Copper(II) saccharinate complex of MT3MP
[Cu(sac)(PToVa)]	Copper(II) saccharinate complex of PToVa
[Cu(sac)(PTSali)]	Copper(II) saccharinate complex of PTSali
[Cu(sac)(PT2AP)]	Copper(II) saccharinate complex of PT2AP
[Cu(sac)(PT2Py)]	Copper(II) saccharinate complex of PT2Py
$[Cu(sac)(PT24D)(H_2O)]$	Copper(II) saccharinate complex of PT24D
[Cu(sac)(PT3MP)]	Copper(II) saccharinate complex of PT3MP

CHAPTER I

INTRODUCTION

1.1 Structure and Historical Background of Saccharin

Saccharin is one of the most widely used artificial sweetening agents. It is known as *o*-sulfobenzimide or 1,2-benzothiazole-3(2H)-one 1,1-dioxide. The structure of saccharin is shown in Figure 1.



Saccharin is about 500 times sweeter than saccharose and is being used as a sugar substitute especially for diabetics (Jovanovski *et al.*, 2000). It has a low solubility in water and is normally used in the form of sodium or calcium salt (Mazur *et al.*, 1983). Its sodium salt is soluble in most organic solvents (Haider *et al.*, 1983) hence it is widely used as a non-caloric artificial sweetening agents as the sugar substitution can reduce the caloric intake (Nabors *et al.*, 1991).

Saccharin was first discovered accidentally by Fahlberg in 1878 during investigation of the oxidation of *o*-toluenesulfonamide. Further research was conducted by him and Remsen and they published articles on saccharin, one year later (Baran *et al.*, 2006). In 1887, saccharin was produced on an industrial scale as a carbohydrate-free sweetening agent (Schulze *et al.*, 1997) and continued to be used as an important low caloric sweetener until early 1970s. However, the uses of saccharin as a food additive was banned as studies showed that it caused urinary bladder carcinomas when implanted into rats (Allen *et al.*, 1975). This controversy leads saccharin to be included in the list of potential human carcinogen substances in USA. Further research on the consumption of saccharin towards human population disproved the earlier findings and there was actually no association between cancer and saccharin. The intake of saccharin was deemed safe for humans, hence the ban was lifted by the US FDA in 2000 (Turner *et al.*, 2001) and saccharin remains free from being a potential cancer-causing substance.

Saccharin contains three functional groups that are connected to each other *via* a five-membered ring. They are the carbonyl, imino and sulfonyl moieties with oxygen, nitrogen and sulphur that act as donor atoms (Jovanovski *et al.*, 2000). The coordination chemistry of the saccharin anion is very interesting as these

donor atoms can chelate to the metallic centre with different modes. The coordination of one nitrogen, one oxygen (carbonylic) or two oxygen (sulfonic) atoms to the metal will generate either N- or O-monodentate or bidentate complexes (Baran *et al.*, 2005). The different coordination of the saccharinate anion is shown in Figure 2.

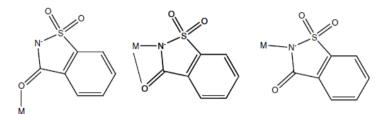
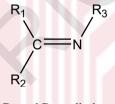


Figure 2: Various coordination modes of the saccharinate anion

1.2 Properties of Tridentate NNS or ONS Schiff Bases

Schiff base is the product that forms from the condensation reaction between primary amines and carbonyl groups (Cimerman *et al.*, 2000). It has the general formula of RHC=N-R', where R and R' can be an alkyl, aryl, cyclo alkyl or heterocyclic group. Figure 3 shows the general structure of the Schiff base.



 R_1 , R_2 and R_3 = alkyl or aryl

Figure 3: General structure of Schiff base

Previous work showed that Schiff bases are chemically and biologically essential because of the lone pair electrons in sp^2 hybridized orbital of nitrogen azomethine group. They are considered as an excellent chelating agent due to the presence of C=N group which has high flexibility. The possibility to form a five or six membered rings with the metal ions are high if the –OH or –SH groups are close to the azomethine group (Ashraf *et al.*, 2011). Schiff bases having chelation with nitrogen, oxygen or sulphur donor atoms can be either bi- or tridentate ligands. These ligands form very stable complexes when chelated to transition metals (Zoubi, 2013) and the complexes with tridentate Schiff base ligand particularly show good antibacterial, antifungal and biological activities (Chohan *et al.*, 2000).

Generally, uses of different aldehydes and ketones produces a variety of Schiff bases with combination donor atoms for instance NS, NNS or ONS ligands. These Schiff bases exhibited interesting physical and chemical properties and the interactions of thiosemicarbazone Schiff bases with any transition metal ions form complexes of different geometries and properties. These donor atoms determine the coordination structure of the complexes hence affects the biological properties of the compounds. It was found that complexes derived from hydrazones exhibited stronger activity as metal ions chelate to pyridine ring compared to coordination to the azomethine nitrogen atom (Bernhardt *et al.*, 2008).

Cytotoxic and biological tests were carried out on metal complexes of tridentate NNS/ONS ligands showed that the complexes have been found to be biologically active. For example, Hossain *et al.*, (1996) carried out antimicrobial tests on the copper(II) complexes of the 2-acetylpyridine Schiff base of S-benzyldithiocarbazate on various types of fungi and bacteria. It was found that the chelation of the tridentate NNS Schiff base to the copper(II) ion enhanced the antifungal activities. Tarafder *et al.*, (2000) also reported similar work with tridentate ONS Schiff base derived from condensation of S-benzyldithiocarbazate with salicylaldehyde exhibited strong antimicrobial activity against bacteria.

1.3 Metal Complexes of Saccharin

Metal complexes of saccharin have earned an important role in coordination chemistry. The ability of saccharin to act as a polyfunctional ligand led to many studies on its metal complexes especially with the first row transition metals (Henderson *et al.*, 1999). Most of the synthesized and investigated metal complexes were initially mixed aqua-saccharinato species. But the versatility of saccharin to chelate *via* various modes has brought to many other great numbers of simple and mixed-ligand complexes. Most of these complexes have the deprotonated saccharin in the form of nitranion or saccharinate anion (Figure 4). It is identified as sac while the free saccharin itself is known as Hsac (Baran *et al.*, 2006).

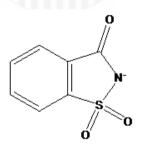


Figure 4: Structure of the saccharinate anion

Saccharin acts as a monodentate ligand by using its nitrogen, sulfonyl oxygen or carbonyl oxygen atoms or as a bidentate ligand by using either two donor atoms. But coordination by its nitrogen is most common and usually observed in complexes of this general molecular formula, $[M(sac)_2(H_2O)_4].2H_2O$, where M are first row transition metals (Ravoof *et al.*, 2004). The reaction of sodium saccharinate with these divalent metal ions from V(II) to Zn(II) produced isomorphous coordination compounds (Baran *et al.*, 2006). According to Jovanovski, the nitrogen atom is found to be more negatively charged than the carbonyl oxygen atom due to its coordination mode is in the solid state. The $[M(sac)_2(H_2O)_4].2H_2O$ complex adopted an octahedral geometry with two *N*-bonded saccharin ligands in the *trans* position, as shown in Figure 5.

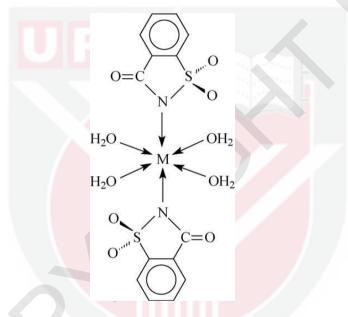


Figure 5: Structure of [M(sac)₂(H₂O)₄].2H₂O complexes

(M^{II}= V, Cr, Mn, Fe, Co, Ni, Cu and Zn)

 $[M(sac)_2(H_2O)_4].2H_2O$ species usually acts as precursors for synthesizing mixedligand saccharinate complexes with these metal cations. The presence of aqua ligands in the complex can be removed by neutral ligands as it is very labile. Therefore the complexes are easily synthesized by the reaction between a neutral ligand and the aqua-saccharinato complex in solution. All of the four aqua ligands in the complex will be substituted by the ligands hence forming stable mixedligand complexes (Baran *et al.*, 2006).

1.4 Biological Effects of Metal Saccharinate Complexes

Systematic studies on saccharin and its metallic complexes have attracted researchers because of its suspected carcinogenicity (Baran *et al.*, 2005). Saccharin was initially thought to cause urinary bladder carcinomas in mice, consequently much research has been carried out to investigate the health risks of saccharin consumption towards humans. Saccharin has been reported to have potential as an inhibitor for certain enzyme reaction. Such compounds containing heterocyclic sulphonamides as ligands behaved as potent inhibitors of the zinc enzyme carbonic anhydrase (Supuran, 1996). Carbonic anhydrase is a family of zinc metalloenzymes that catalyze carbon dioxide into hydrogen carbonate. This enzyme acts as a modulator of aggressive tumor behaviour and as a marker for detecting several cancers (Mahon *et al.*, 2015). The complexes [Zn(sac)₂(H₂O)₄].2H₂O and [Cu(sac)₂(H₂O)₄].2H₂O have been reported to show an inhibitory effect over carbonic anhydrase (Supuran *et al.*, 1992).

Saccharinato complexes have also been studied to have superoxide dismutase-like behaviour (SOD). SOD is one of the most powerful natural antioxidant enzymes that is found in all living cell, which catalyze the dismutation of the superoxide radical into either oxygen or hydrogen peroxide molecule (Baran *et al.*, 1990). It was first reported to have copper in the living system by Mann and Keilin in 1938 while the presence of zinc was discovered years later. There have been reports of superoxide-dismutase like activity of several divalent metal aqua-saccharinato complexes of general formula $[M(sac)_2(H_2O)_4].2H_2O$ where M is the first row transition metallic cation that have been investigated. All of the metal complexes have the ability to dismutate the O_2^- anion, by using nitroblue tetrazolium reduction assay. The results showed that copper saccharinate complexes (Apella *et al.*, 1993).

Saccharin may also be potent as an antidote for metal poisoning (Malik *et al.*, 1984). Although this property has not been further studied in detail, the stability of several polymeric saccharinato complexes shows amazing perspectives towards this issue. The complexes for instance Pb(II), Ti(II) or Ag(II) containing saccharin, suggest that saccharin is useful as a promising ligand for therapies (Baran *et al.*, 1995). Recently, a study lead by Mahon *et al.*, (2015) proved that saccharin could eventually developed into drugs that treat cancer cells including the breast, liver, prostate, kidney and pancrease. The study indicated that saccharin reacts with a certain protein present in aggressive cancer cells. The protein, known as carbonic anhydrase IX (CA IX), regulates pH in and around cancer cells, allowing tumors to thrive and potentially metastasize to other parts of the body. By disrupting this pH balance *via* blocking CA IX activity, it helped these cancer cells from growing and proliferating (Mahon *et al.*, 2015).

1.5 Copper Oxide Thin Films from Metal Complexes *via* the Aerosol Assisted Chemical Vapour Deposition Technique

Aerosol-assisted chemical vapour deposition (AACVD) is a one type of conventional CVD process which is in liquid phase. Precursors are dissolved in a suitable solvent and aerosol is generated by use of an ultrasonic humidifier to create a mist. This mist is then transported to the reactor by a carrier gas which is argon (Jones *et al.*, 2009).

There are two possibilities for a successful thin film deposition. There is a case where the decomposition of the precursor can occur in the gas phase which then leads to the presence of intermediates. These intermediates will become adsorbed to the substrate together with some unaffected vapourised precursor. Further decomposition with heterogenous reactions causes a well adhered thin film of the desired product and a great quality deposition can be obtained. Besides that, in a case where the temperature of the substrate is too high, the decomposition and reaction would occur mostly in the gas phase. This will lead to nucleation of particles and the adsorption of these particles caused the production of porous films on the substrate glass. The schematic illustration of the processes involved in AACVD is shown in Figure 6. (Marchand *et al.*, 2013).

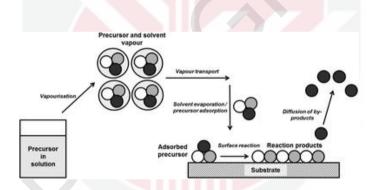


Figure 6: Schematic illustration of AACVD processes

Currently the use of single-source precursor to synthesize semiconductor materials has been widely explored since this precursor could be synthesized in atmospheric conditions (Hamid *et al.*, 2007). The most popular single-source precursors studies are the homo or hetero leptic metal complexes derived from for instance dialkyldithiocarbamates, dialkylchalcogenophosphate, alkylthiourea, dichalcogenoimidophosphinate and others (Kedarnath *et al.*, 2007). The single-source precursors have been chosen because of its air-stability, non-toxic nature and easily controlled stoichiometry. They also produce less unwanted side reactions (Mgabi *et al.*, 2014).

The complexes of S-alkyl/aryl dithiocarbazates are often used as single source precursors because the presence of soft sulfur and nitrogen donor atoms as essential chelating agents (Ali *et al.*, 2008) which were successfully used to prepare various metal oxides and sulphides (Bera *et al.*, 2010). Meanwhile the complexes derived from the thiosemicarbazide ligand where the NS chelates to the metal and acts as a structure-directing agent are effective in classifying the anisotropic structure of the nanocrystals (Nair *et al.*, 2006).

The copper complexes derived from thiosemicarbazide were used as single-source precursors for the deposition of cuprous oxide thin film. The deposition of cuprous oxide thin film has been carried out due to their various applications for example photoelectrochemical (PEC), catalytic, electrochemical and electrochromic applications (Abuzeid *et al.*, 1986). Cuprous oxide (Cu₂O) is one of the important oxide compounds of copper. It is a *p*-type semiconductor that shows various essential properties and has been studied due to their low raw material cost, narrow band gap, non-toxic nature and interesting electrical and optical properties (Hara *et al.*, 1998).

Generally, there have been reports that thiosemicarbazones metal complexes have shown good potential as anticancer agents. With the strong biological effect of saccharin and the NNS/ONS ligands, the saccharinate complexes synthesized in this work are hoped to be biologically relevant and may have potential to inhibit the cancer cells. Copper(II) was chosen as the metallic centre due to its presence in enzymes that are essential in human's body. Its complexes have proven to be excellent candidates for the biological applications due to their binding ability (Liang *et al.*, 2003). It is also hoped that the copper complexes can be deposited into copper oxide thin films and has the ability in various purposes such as photoelectrochemical, photoelectrocatalytic, electrical, and optical studies, in future. Hence, the photocurrent performance of the thin films is conducted and hoped to be potent for these studies. Therefore, the synthesis, characterization and applications of new mixed-ligand copper complexes containing saccharin derived from thiosemicarbazones and tridentate NNS/ONS Schiff bases are reported in this work.

1.6 Objectives

The objectives of this project are:

- 1. To synthesize Schiff bases derived from 4-methyl-3-thiosemicarbazide, 4ethyl-3-thiosemicarbazide and 4-phenyl-3-thiosemicarbazide.
- 2. To synthesize new mixed-ligand copper complexes by reacting $[Cu(sac)_2(H_2O)_4].2H_2O$ with appropriate Schiff bases and to characterize the complexes by various physico-chemical techniques.
- 3. To evaluate the cytotoxic activity of the synthesized compounds against human breast cancer cell lines.
- 4. To synthesize copper oxide thin films deposited by AACVD method and to study the photocurrent activity of the thin films.

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