



A REVIEW ON THERAPEUTIC APPLICATION OF PALLADIUM COMPLEXES

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Abstract

Platinum-based metallodrugs, e.g. cisplatin, oxaliplatin, carboplatin, have been successfully used as effective anticancer drugs in the clinical treatment of cancer. These derivatives are being used for more than 50% of treatment regimens worldwide for cancer patients.[1–3] However, their remarkable success is marred by clinical limitations, including acquired or intrinsic resistance problems, limited spectrum of activity, less target specificity and high toxicity leading to side effects. These limitations have stimulated us to design and synthesize new metal-based drugs with more effectiveness, less toxicity, target specificity and preferably non-covalent DNA binding

Keywords: Palladium Complexes, Crystal structure, DNA-interaction, Cytotoxicity.

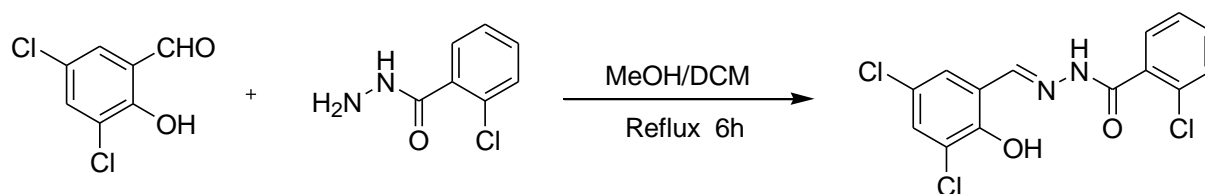
Introduction

In medicinal chemistry, metal complexes considerably gained development over the last decades. All of the metal complexes, transition metal complexes are widely used as the chemotherapeutic agents and also plays a major role in cancer treatment.¹ Schiff bases are essential category of organic compounds and it can applied in several fields like biological, clinical medicinal. Heteroaryl compounds of hydrazone Schiff bases have extra chelating center such as C=O along with function group. So these binding centers act as a multi dentate ligands and it can coordinate with different metal ions. So that Hydrazone and their chelates are shows antibacterial and antiviral activity. So, it is utilized for the remedy for tumour.² Cancer is the major cause of mortality, cancer cells can able to multiply rapidly. Main aim of the cancer drugs is to destroy the DNA. Cisplatin is an anti-cancer drugs used for the treatment of the various types of cancer. It shows the activity against various types of tumour.³ Compounds of Pd(II) has many applications in cross coupling

reactions. Heterocyclic ligands combine with Pd metal to form new active compounds, which are used for the treatment of cancers. Pd(II) compounds show the anti-cancer activities. In many cases, Pd(II) compounds show more anti-cancer activity than Pt(II) compounds.⁴ New derivatives of hydrazone complexes have a variety of biological activities such as antimicrobial, anticonvulsant, antidepressant, anti-inflammatory, anti-cancer, anti-fungal. Hydrazone metal complexes show pharmacological activity. Palladium complexes are highly cytotoxic to human tumour.⁵ Hydrazone complexes are organic compounds, comprising -NH-N=CH- group in the structure. In transition metal complexes, Pd azomethine complexes have extra beneficial properties in the medical field. So, Pd(II) derivatives have been used for anti-cancer drugs because of their potential pharmacological properties. Palladium complexes with aromatic heterocyclic ligands such as derivatives of pyrimidine, quinoline exhibited anti-tumour activities.⁶ Schiff bases have significant effects in the medical field. Schiff bases are highly preferred ligands due to their ability to stabilize metals in different oxidation states. Transition metal complexes have significant potential in biomedicine and biochemistry applications due to their well-defined biological system model and unique properties. They can be easily obtained using mild reaction conditions.⁷ Designing of ligands has also great importance for the development of anti-cancer agents.⁸ Imidazole is a main class of compounds, which are found in different natural and pharmaceutical products. Not only that, substitution of synthetic with imidazole has various biological activities such as anti-inflammatory, anti-bacterial effects. Sharma introduced the imidazole compound modulating the pro-survival NF- κ B pathway and sensitizing cancer cells towards DNA damaging agents.⁹ Metal complexes containing sulfur-nitrogen chelating agents have biological activities. Hydrazone ligands formed from dithio carbazates and chromones that are used for the generation of supramolecular structures and they show beneficial pharmacological properties.¹⁰ Schiff base metallo drugs show their effective bioactivity against bacterial and parasitic species. Schiff bases are commonly derived from condensation reaction between amine and aldehyde. It can coordinate metals through imine nitrogen and another group.¹¹ Hydrazone derived Schiff bases of dehydroacetic acid act as active chelating agents.¹²

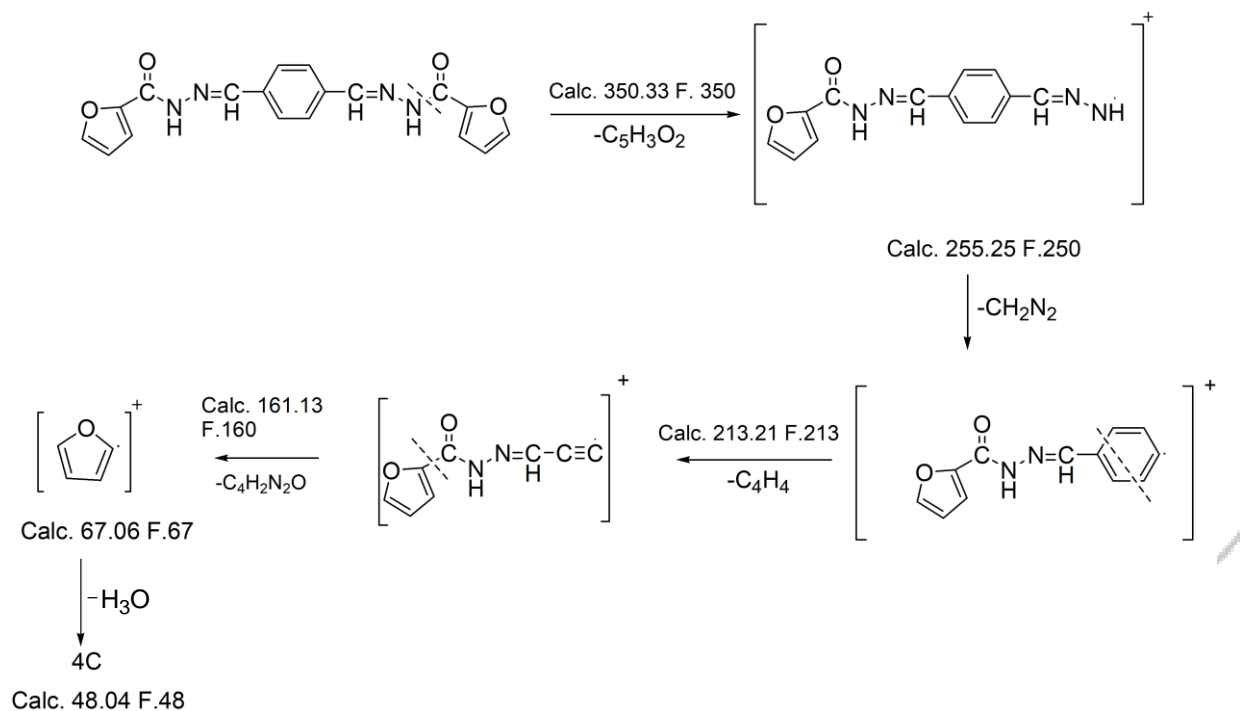
SCHEME-1

This article deals with the synthesis of two biologically active complexes, which are synthesized by using 2-chloro-benzoic acid (3,5-dichloro-2-hydroxy-benzylidene)-hydrazide (1) ligand. One of the complexes and the ligand, molecular structure confirmed by XRD. It reveals that the ligand coordinated to Pd metal through ONO chelation. Synthesized compounds show the intercalation mode of binding. Interaction study of complexes with bovine serum albumin shows that, compounds bind strongly with BSA. Compounds also show anti-oxidant activity and MTT assay revealed that, Pd (II) complexes show activity against HeLa and MCF-7 cancer cell lines. So these complexes are used as anti-cancer agents.¹³



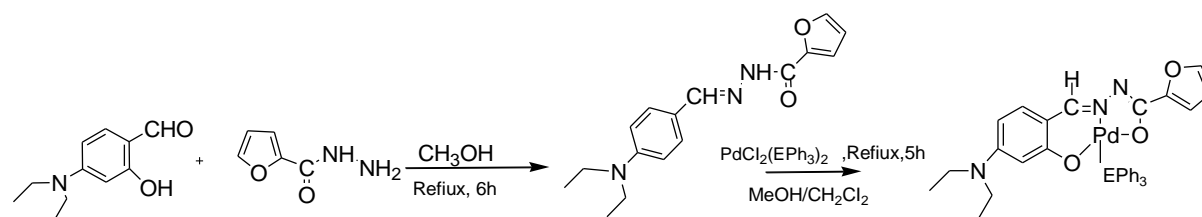
SCHEME-2

This article deals with the synthesis of Furo-(phenyldimethine)-carbohydrazone(H₂L) by condensation reaction of 2-furonic acid hydrazide with tetraphthaldehyde in 2:1 molar ratio. Reaction of ligand (H₂L) with chloride salts of Co (II), Ni (II), Cu(II), Ru (II) and Pd (II) ions leads to the formation of octahedral and square planar complexes. Chleates was structurally characterized by various analytical and spectral techniques. Stoichiometry of chelates in 1:1,1:2 and 1:3 molar ratio leads to the formation of sandwich, binuclear and trinuclear complexes. Basis of molar conductance values, complexes shows that non-electrolytic in nature. Based on IR data, ligand served as tetradentate in a neutral keto form. Ligand coordinated to metal ions through oxygen atoms Biological data indicated that all the complexes have cytotoxic and anti-oxidant activity. ¹⁴



SCHEME-3

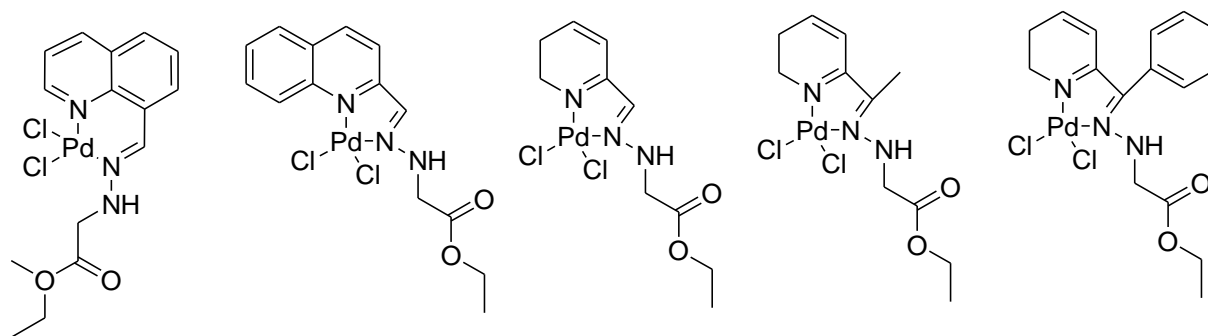
This article deals with the synthesis of pd (II) complexes of N¹-(4-diethylamino)-2-hydroxybenzylidene) furan-2- carbohydrazone. Characterization of complexes was done by spectral methods. Using single crystal x-ray diffraction, structure of one of the complexes determined. Using UV-Visible and fluorescence titration, DNA and protein binding affinities was examined. MTT assay method shows that, the in-vitro cytotoxicity of the compounds against AS49 (lung cancer) and MCF7 (breast cancer). ¹⁵



SCHEME-4

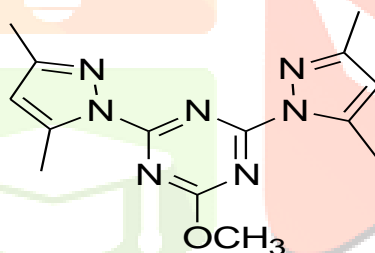
Snezana k. Bjelogrić and co-workers checked the anti-cancer activity of Pd complexes 1-5 with bidentate N-heteroaromatic hydrazone ligand. For the Pd (II) complexes with condensation of ethyl hydrazinoacetate and quinoline-8-carboxaldehyde (complex-I) and 2-for mylpyridine, for which apoptosis

was determined as a mechanism of anti-cancer activity. Investigation revealed that they arrest the cell cycle in G0/G1 phase, Results obtained from circular dichroism and fluorescence spectroscopy shows that these complexes are suitable to be delivered to a blood stream via human serum albumin.¹⁶



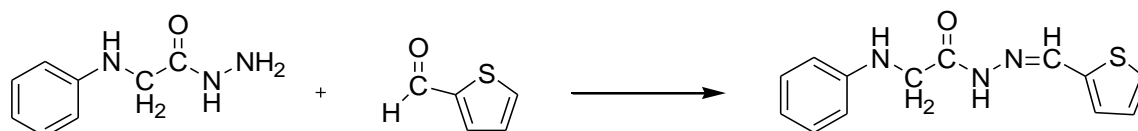
SCHEME-5

Jamal Lasri et al synthesized the complexes by the reaction of 2-methoxy-4,6-bis (3,5-dimethyl-1H-pyrazol-1-yl)-1,3,5-triazine ligand with the palladium chloride in the molar ratio of 1:1 to formed the square planar complex $[Pd(PT)Cl(H_2O)] \cdot H_2O$, using acetone as a solvent. These complex stabilized by inter and intramolecular hydrogen bonding. Normally, reaction proceed through C-N cleavage, it connected the pyrazole and s-triazine. The palladium based drugs used as the anti-cancer agents.¹⁷



SCHEME-6

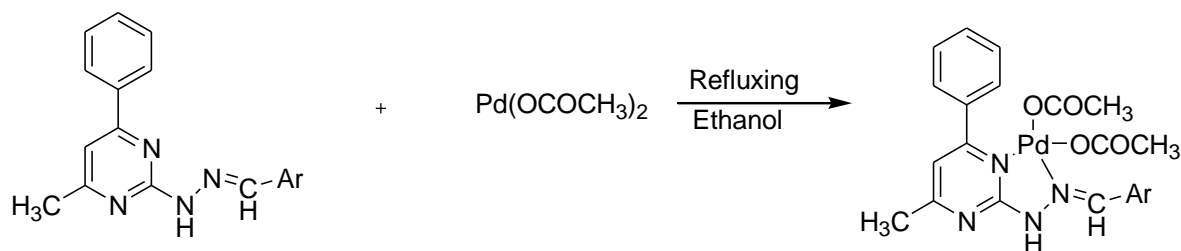
S.A Aly and S.K fathalla mainly focused on the synthesis of Pd (II), Cd(II), Cu(I) based polydentate Schiff base ligand. They are ((Z)-2-(phenylamino)-N¹-(thiophen-2-ylmethylene)acetohydrazide). Metal complexes and ligand are characterized by molar conductance, elemental analyses and spectral analysis. Using molecular mechanic calculations, possible structure of metal complexes obtained. Complexes of Pd (II), Cd(II), Cu(I) and the ligand revealed the excellent antioxidant properties and fighting against cancerous cells. As compared to the parent compound of Cu (II), Cu(I) complexes has stronger antioxidant effects.¹⁸



SCHEME-7

New palladium complexes of 2-arylidene-1-(4-methyl-6-phenyl-pyrimidin-2-yl) hydrazines are synthesized by the kiran singh and team. Complexes are characterized by IR, ¹H-NMR, UV-Visible, fluorescence and thermogravimetric analysis. In vitro antibacterial activity test done against two gram-

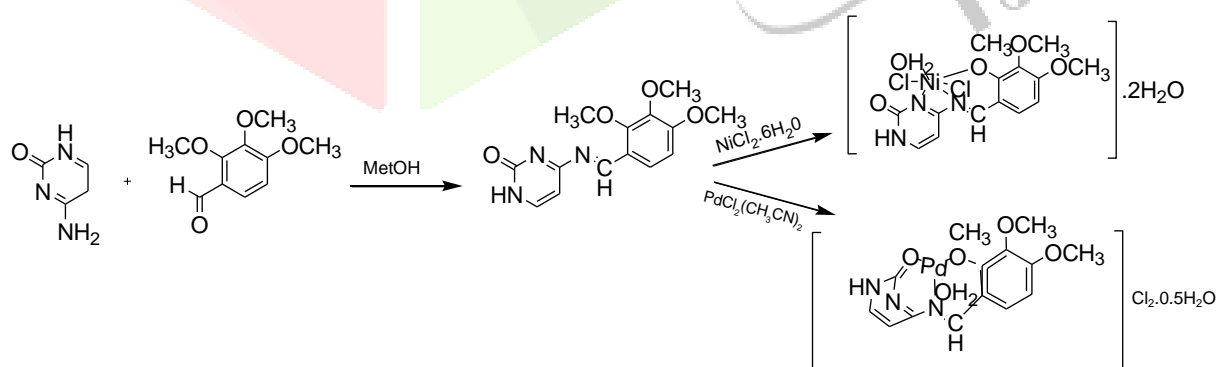
positive bacteria and two gram-negative bacteria. Using two fungal strains, antifungal activity of the ligands checked. Interaction between ligand and Pd (II) complexes with bovine serum albumin determined by fluorescence spectroscopy. Using emission spectra, it revealed that complexes interact strongly with BSA protein than their parent hydrazones.¹⁹



SCHEME-8

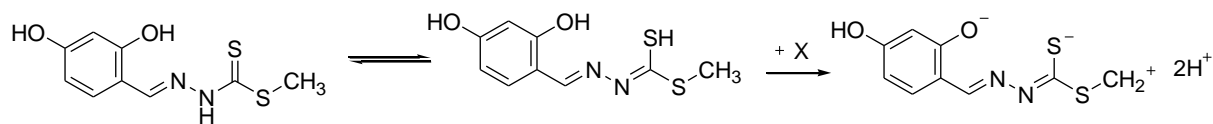
Mehmet Esref Alkis and his co-workers performed by the synthesis of New Schiff base ligand using 4-amino pyrimidine-2(1H)-one and 2,3,4-trimethoxy benzaldehyde. Reaction of ligand with NiCl₂·6H₂O PdCl₂(CH₃CN)₂ to formed the Ni(II) and Pd(II) complexes. Complexes are characterized by elemental analysis, ¹H, ¹³C-NMR, FT-IR, UV-VISIBLE, magnetic susceptibility, thermal analysis and XRD. Antiproliferative activity of synthesized Ni(II) and Pd(II) complexes and ligands tested on HepG2. Using MTT analysis method, biocompatibility tested. Cytotoxic activities are tested in HepG2 cancer cells. On the basis of MTT method, synthesized ligands did not exhibit antiproliferative activity. But, Ni(II) and Pd(II) complexes exhibit antiproliferative activity. As compared to both Ni(II) complexes has stronger antiproliferative activity. Combined application of EP + compounds is much more effective than the usage of compounds alone for the treatment of HepG2 cancer cells. So,

Ni (II) and Pd(II) complexes have potential for the treatment of cancers and used as the anti-cancer agent for the treatment of hepatocellular carcinoma.²⁰



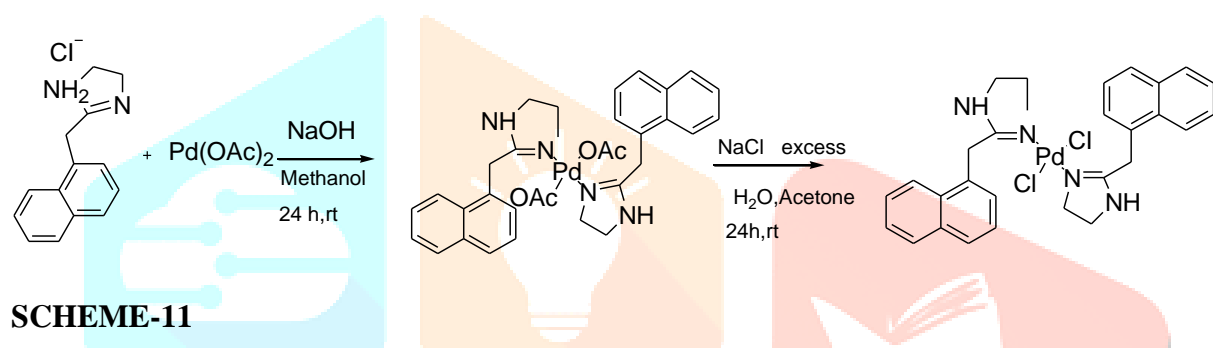
SCHEME-9

The [M(PPh₃)(L)CH₃OH], [Pt(PPh₃)(HL)Cl] and Ru(CO)(PPh₃)₂(L) complexes were synthesized and it is characterized by FTIR, NMR, ESI-MS and UV-Vis spectroscopy. Molecular Structure of one and two confirmed by single crystal x-ray crystallography. Anti-oxidant activity were tested using DPPH(2,2-diphenyl-1-picrylhydrazyl). In vitro cytotoxicity of complexes checked on breast cancer colon cancer, liver cancer and normal lung fibroblast cell lines.²¹



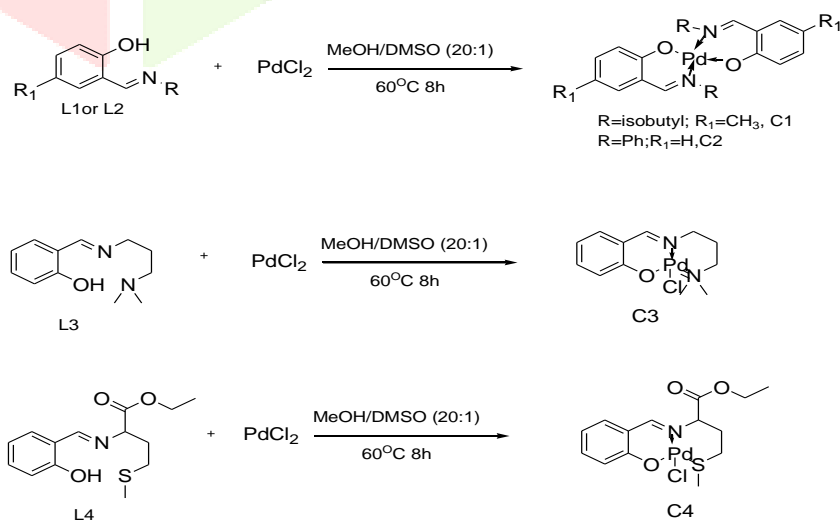
SCHEME-10

The 2-(naphthalen-1-yl methyl)-4,5-dihydro-1H-imidazole, hydrochloride were synthesized. Characterized by elemental analysis, spectroscopic methods and single crystal x-ray structure analysis. Cytotoxicity of Naphcon and Pd (II) complex checked in vitro against human breast and cervical epithelial carcinoma cancer cells. Interaction of Naphcon and Pd (II) complex determined using bovine serum albumin by absorption and fluorescence spectroscopy. In this method, the binding constant (k_b) determined using spectroscopic methods. Binding site of Pd (II) complex and Naphcon was found to be located on site III and I of BSA.²²



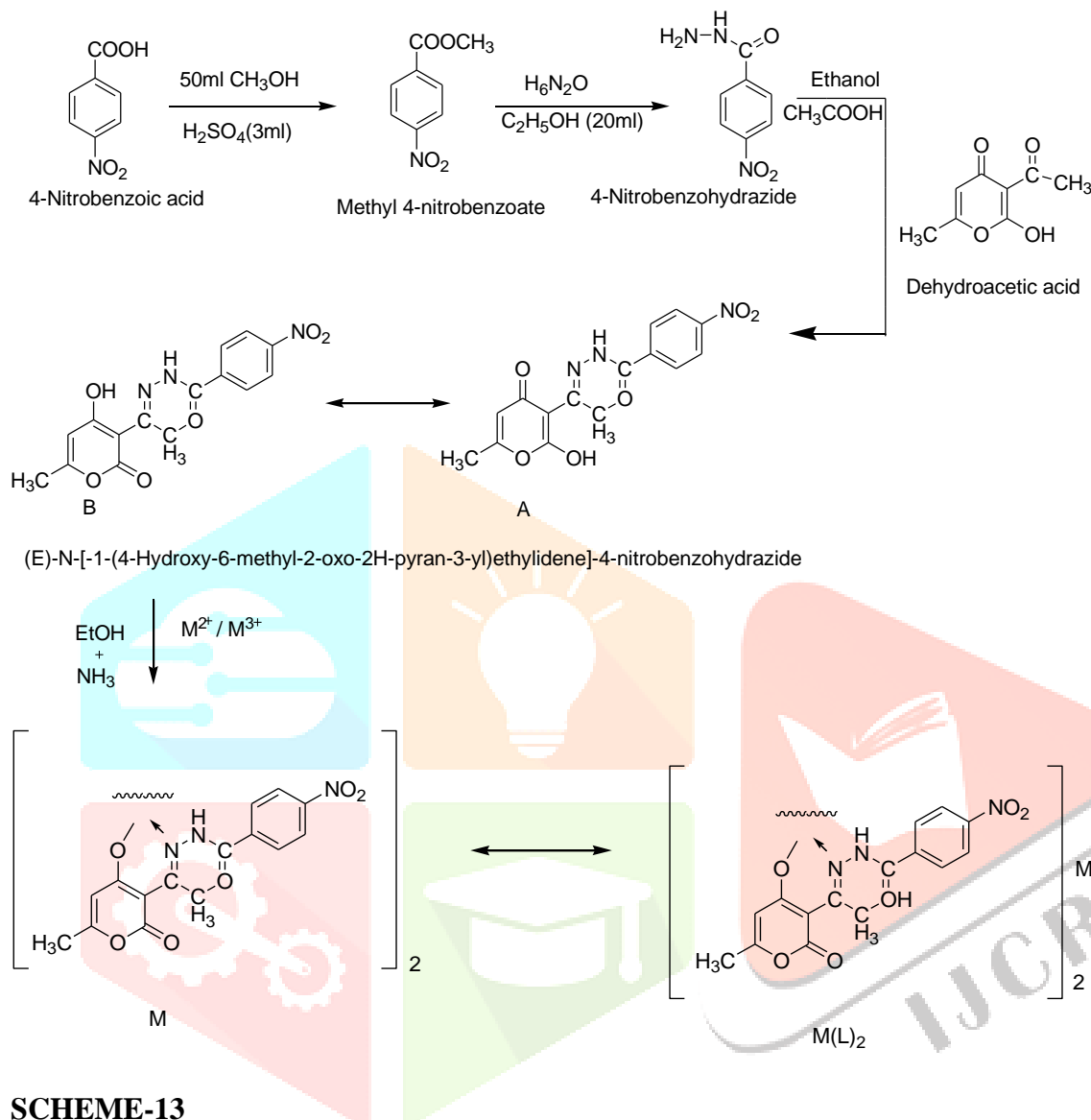
SCHEME-11

The Pd(salicylaldimine)₂, Pd(salicylaldimine)Cl and methionine derived ligand based Palladium complexes were synthesized. It was characterized by ¹H, ¹³C NMR spectroscopy, high resolution electrospray mass spectrometry, single X-ray analyses. In vitro cytotoxicity performed in non-small cell lung (A549) and hepatocellular (HepG2) cancer cells. MTT assay revealed that these type of Pd complexes suppress cancer cell viability.²³



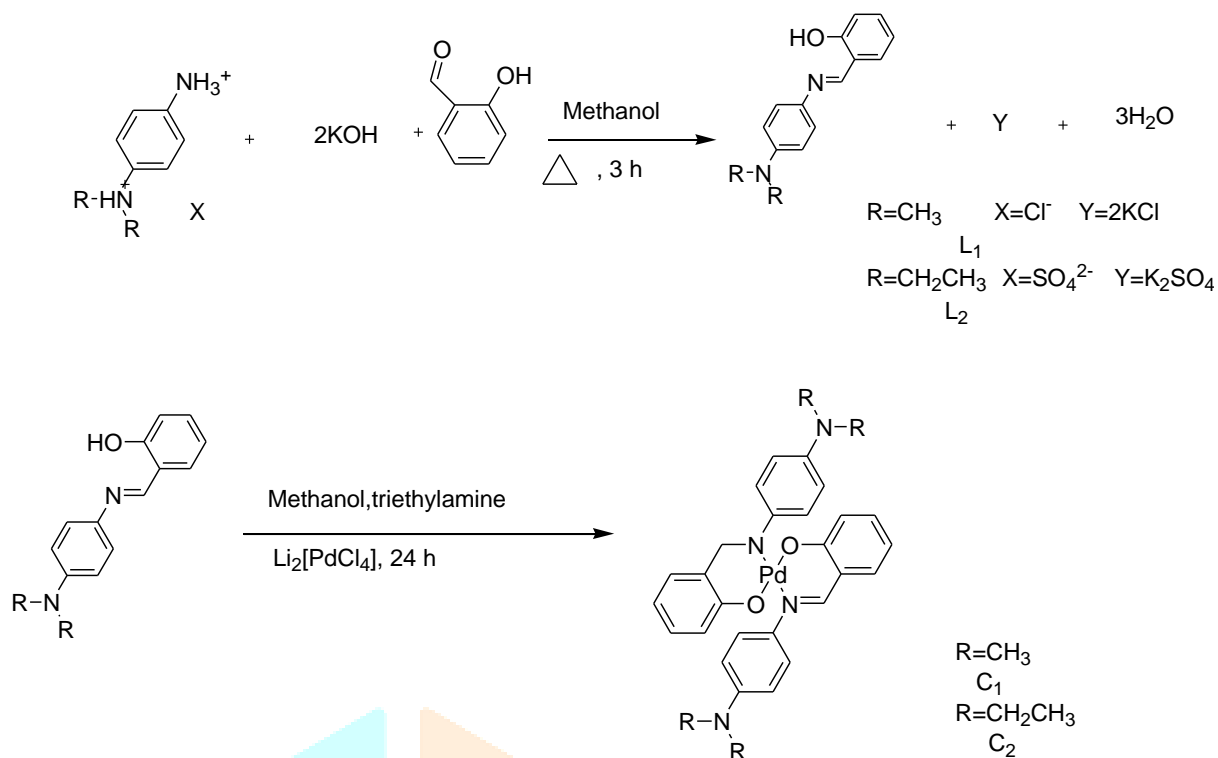
SCHEME-12

Hydrazone derived ketimine of dehydro acetic acid and its metal [Cu(II),Ni(II),Zn(II) Fe(III),Cd(II),Pd(II),La(III),Ce(III) complexes were synthesized. These are characterized by IR, $^1\text{H-NMR}$ and $^{13}\text{C NMR}$ and UV-Vis spectroscopy. Using absorption spectroscopy, DNA studies are carried out. Cu(II) ,Zn(II) and Pd(II) complexes has significant activity against HeLa cells(cervical cancer).²⁴



SCHEME-13

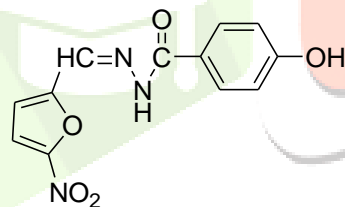
Reaction with salicylaldehyde and N,N-dimethyl-p-phenylene diamine to formed the new Pd(II) complexes with Schiff bases. Ligands and complexes were characterized by elemental analysis, IR and UV-vis spectroscopy, ^1H , $^{13}\text{C-NMR}$, thermogravimetry and differential thermal analysis. Formation of N,O-chelate with the pairs of phenolate O and imine N occupying the trans positions showed by crystal structure data.²⁵



Synthetic route for schiff bases(L₁ and L₂) and corresponding palladium(II) complexes(C₁ and C₂)

SCHEME-14

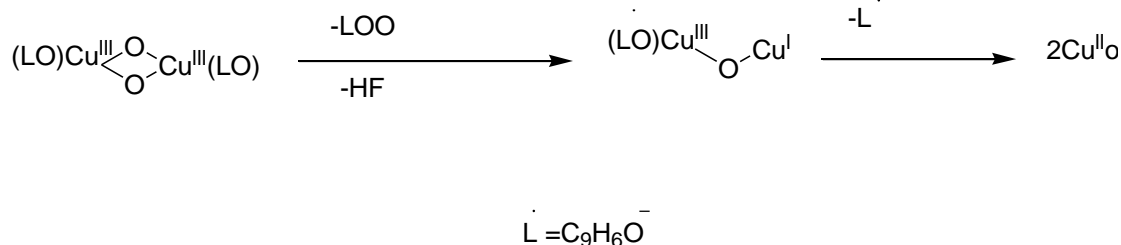
M.Y Nassar and co-workers prepared new mononuclear complexes of Pd(II), Ag (I), Pt (IV) and Hg(II) with Nifuroxazide. It is prepared by the reaction of metal salts with the drugs. Complexes were characterized by elemental and thermal analysis and FT-IR, ¹H-NMR and UV-Vis spectra. Complexes used as the drugs for breast cancer (MCF7).²⁶



Chemical formula of Nifuroxazide(Nif)

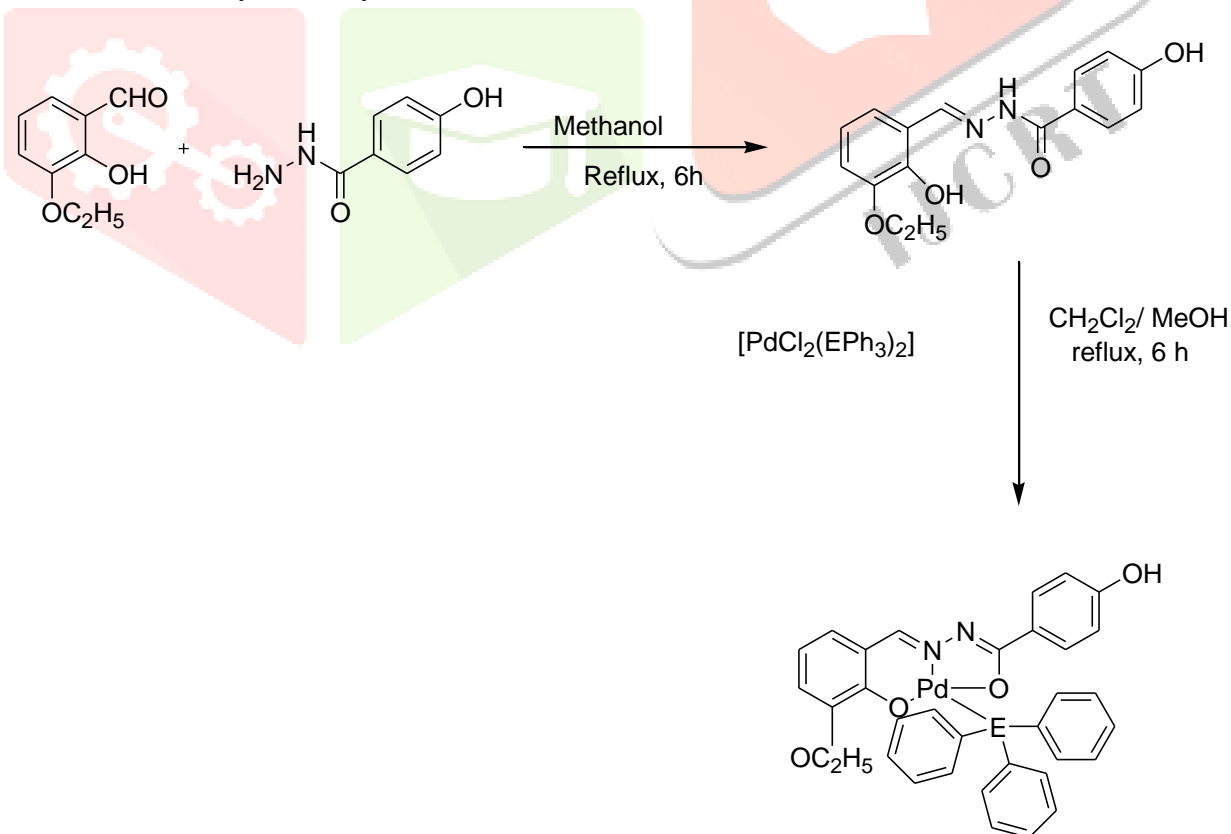
SCHEME-15

Reaction of Na_2PdCl_4 and $\text{CuCl}_2 \cdot \text{H}_2\text{O}$ with fluoridated enaminone ligand to formed the complexes of Pd (II) and Cu(II). These complexes were characterized by elemental analysis, FT-IR spectra, $^1\text{H-NMR}$ spectra. Anti-Cancer activity of these complexes tested against breast cancer cell line (MCF-7) and liver cancer cell (HepG2). So, found that $\text{Cu}_2(\text{diCO})_4$ complex has activity against human liver cancer cells.²⁷



SCHEME-16

Reaction of 4-hydroxy benzoic acid hydrazide ligand to formed the new Pd (II) complexes $[\text{Pd}(\text{pph}_3)\text{L}]$ and $[\text{Pd}(\text{Asph}_3)\text{L}]$. Structure of complexes determined by single crystal x-ray diffraction, that revealed the complexes have square planar geometry. In vitro biological studies are done using UV-Visible absorption spectroscopy, emission spectroscopy, cyclic voltammetry and viscosity measurements. UV-Vis and fluorescence spectroscopy, give the interaction between ligand and complexes. Complexes interact with BSA protein more strongly than the parent ligand done by the absorption and emission spectra. Using MTT assay method, In vitro cytotoxicity were checked to tumour cell lines (HeLa and MCF-7).²⁸



synthesis of ligand and palladium(II) complexes.

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