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SYNTHESIS, SPECTRAL AND BIOLOGICAL STUDIES OF MIXED LIGAND TRANSITION METAL COMPLEXES OF NITROKETENE DITHIOACETAL WITH EPHEDRINE

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Abstract:

Metal ions play an important role in bioinorganic chemistry. Metals such as iron, cobalt, nickel, copper and zinc may exist in trace amounts in biological systems. Also, metal has played an important role in medicine for years; Metal ions play a vital role in a vast number of widely differing biological processes. They have a considerable effect in biological processes and depending on their concentration; they may either contribute towards the health of the organism or cause toxicity [35]. Also, metal has played an important role in medicine for years; many are essential in human diet in varying amounts and some are used in the medical profession as invaluable diagnostic tools. Metal ions play a vital role in a vast number of widely differing biological processes. They have a considerable effect in biological processes and depending on their concentration; they may either contribute towards the health of the organism or cause toxicity [1]. Ephedrine is a synthetic sympathomimetic amine [8,9] acts on part of the sympathetic nervous system (SNS). In synthetic organic chemistry, the nitroketene dithioacetal motif (NKDA) based organo sulfur compounds are well known intermediates as a two carbon push–pull system.[10,11] The nitro group acts as a powerful electron-withdrawing group and the two alkylated sulfur atoms readily donate their lone-pair of electrons to make the entire NKDA motif frame work as highly polarized system.(1-7) Thorough literature search in the field of nitroketene dithioacetal chemistry showed that there is no report that NKDA has been used as inorganic ligand. It made a new route of synthesizing transition metal complexes with Nitroketene dithioacetal as one ligand which is an organic moiety. The synthesized mixed ligand transition metal complex with drug like ephedrine is also a new novel route in inorganic chemistry. The drug activity can be improved by changing it into new complexes. The biological activity of the drug molecules were compared with the synthesized metal complexes and found that the complexes show better antibacterial activities than the drug ephedrine. Also Central nervous system studies were carried out with synthesized complexes and found that the complexes have CNS depressant activities.(12,13) Hence as a future work the complexes those were synthesized can be used as CNS depressant drugs. The structure of the synthesised complex were characterised using UV, IR, 1H, 13C NMR spectral, EDX analysis, C,H,N elemental analysis and fab-mass spectral analysis.

Key words: *Metal-drug complexes, Ephedrine, Nitroketene dithioacetal, antibacterial studies, Central nervous system activity.*

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INTRODUCTION:

Metals have been used in the treatment of diseases of humans since ancient times. The Chinese were using elemental gold for the treatment of diseases, a practice known as chrysotherapy, as far back as 2500 BC [14]. In more recent times, a stable metal coordination complex based on the element platinum, *cis*-[PtCl2(NH3)2] (cisplatin), has become the most well known of all metal based drugs and hundreds of articles have been published on the synthesis and activity of complexes derived from the parent cisplatin molecule. Since Rosenberg's initial discovery of cisplatin in 1969[15], many more examples of metal-containing drugs have been reported in the literature. Gold containing complexes such as auranofin are commonly used to treat rheumatoid arthritis[16], radiopharmaceuticals based on metals such as technetium and rhenium are used in imaging and radiotherapy[17], and ruthenium complexes have had some success as anticancer drugs[18]. Complexes containing gadolinium, cobalt, lithium, bismuth, iron, calcium, lanthanum, gallium, tin, arsenic, rhodium, copper, zinc, aluminum and lutetium have all been used in medicine [19]. Metal ion plays important role in biology which has lead to the development of huge number of metal complexes with diverse therapeutic activity. The advances in the field of chemistry provide better opportunities to use metal complexes as therapeutic agents. Cisplatin, carboplatin and oxaliplatin are the well known metal-based drugs widely used in treatment of cancer. Besides these complexes other metal complexes have shown promising results in the treatment of diseases like diabetes, ulcer, rheumatoid arthritis, inflammatory and cardiovascular diseases etc. Medicinal applications of metals have played an important role in medicine since thousands of years. Many essential metal ions in our diets in varying quantities are essential, although its significance has been recently realized, which could probably be attributed our increased awareness of personnel and families' health. Metal complexes or coordination complexes, is an atom or ion usually metallic, bonded to a surrounding array of molecules or anions, which are in turn known as ligands or complexing agents.

1.1 Metal complex in the body

Metal ions bound with ligands in some process, and to oxidize and reduce in biological systems. The important metal present in the body is iron which plays a central role in all living cells. Generally iron complexes are used in the transport of oxygen in the blood and tissues. The heme group is metal complex, with iron as central metal atom, which bind or release molecular oxygen [20]

1.2 Metal complex in cancer treatment

Metal complexes have a higher position in medicinal chemistry. The therapeutic use of metal complexes in cancer and leukemia are reported from the sixteenth century. In 1960 an inorganic complex cisplatin was discovered, today more than 50 years, it is still one of the world's best selling anticancer drug. Metal complexes formed with other metals like copper, gold, gallium, germanium, tin, ruthenium, iridium was shown significant antitumor activity in animals. Formation of DNA adducts with cancer cell and results in the inhibition of DNA replication. In the treatment of ovarian cancer ruthenium compounds containing arylazopyridine ligands show cytotoxic activity. Now a day's metal complex in the form of nanoshells are used in the treatment of various types of cancer.[21]

1.3 Metal complex in neurological disorders

Metal complexes are also play a vital role in the treatment of various neurological disorders. Lithium on complex with drug molecules may cure many nerve disorders like Huntington's chorea, Parkinsonism, organic brain disorder, epilepsy and in paralysis etc. Other transition metals such as copper and zinc are involved as a transmitter in the neuronal signaling pathways. [22]

1.4 Metal complex in diabetes

In diabetes intake of chromium metal complex shown considerable reduction in the glucose level. Insulinomimetic zinc complex with different coordination structures and with a blood glucose lowering effect to treat type 2 diabeties. [23]

1.5 METAL-BASED DRUGS

The developments of more potent metal-based drugs have been investigated over the last three decades and it has been discovered that inorganic compounds have enormous impact in medicine [24]. Some metal complexes have been found to have antimicrobial and antiviral properties and could be effective against diseases [25]. This had led to numerous investigations on metal-drug interactions and more studies on metal complexes with the aim of discovering more effective chemotherapeutic agents to fight diseases. Also, it is known that some drugs act via chelation or by inhibitory metalloenzymes but for most drugs that act as potential ligands, a lot of studies are being carried out to know how metal binding influences their activities[26] . Development of inorganic drugs is broadly divided into two categories: diagnostics and therapeutics. As diagnostics, researches are been undertaken in radiopharmaceutical (γ,β+), magnetic resonance

imaging (MRI) and X-ray contrast agents. As therapeutics, inorganic compounds are used as chelating agents, as radiopharmaceuticals (α, β, Auger e-, NC) and as chemotherapeutics, anticancer agents, metal-mediated antibiotics, antibacterial, antiviral, antiparasitic, treatment of rheumatoid anthritis and radiosensitizers[27-29]. Ephedrine is used for temporary relief of shortness of breath, chest tightness, and wheezing due to bronchial asthma. Ephedrine is a decongestant and bronchodilator. It works by reducing swelling and constricting blood vessels in the nasal passages and widening the lung airways, allowing you to breathe more easily. Ephedrine is a sympathomimetic amine commonly used as a stimulant, concentration aid, decongestant, appetite suppressant, and to treat hypotension associated with anaesthesia. Ephedrine is similar in molecular structure to the well-known
drugs phenylpropanolamine and methamphetamine as well as to the important neurotransmitter epinephrine (adrenaline). Chemically, it is an alkaloid with a phenethylamine skeleton found in various plants in the genus *Ephedra* (family Ephedraceae). It works mainly by increasing the activity of norepinephrine (noradrenaline) on adrenergic receptors.[30] It is most usually marketed as the hydrochloride or sulfate salt. Ephedrine, a sympathomimetic amine, acts on part of the sympathetic nervous system (SNS). The principal mechanism of action relies on its indirect stimulation of the adrenergic receptor system by increasing the activity of noradrenaline at the postsynaptic α- and β-receptors.[31] Also the steric orientation of the hydroxyl group is important for receptor binding and functional activity.[32] Ephedrine is a synthetic sympathomimetic amine (33,34) that does not possess the catechol nucleus and is therefore not metabolised by COMT. It is the active ingredient of the plant Ma Huang and it has been used for centuries in China. Ephedrine stimulates both a-receptors and acts both directly and indirectly. Its effects are similar to those of adrenaline, although they persist longer. Ephedrine can be given orally as it resistant to MAO,(monoamine oxidase) the dose is 15-50mg. The history of ephedrine is therefore of more than usual interest. Apart from the historical aspect, ephedrine has been the object of a great deal of investigation on the part of laboratory workers and clinicians. The result has been not only the discovery of unanticipated uses for the drug but—of greater ultimate importance—a renewal of interest in the problem of the relation of chemical composition to physiological actions, and the direction of attention to the incompleteness of our knowledge concerning the mode of action of sympathomimetic drugs (i.e, those which produce effects similar to the result of excitation of sympathetic innervations). It is now quite certain that ephedrine, in spite of its present popularity, is far from ideal in certain respects. In the search for other remedies of this sort important progress has already been made, and undoubtedly much more lies in the immediate future. As is generally known, ephedrine is an alkaloidal active principle obtained from a Chinese herb which, under the name of Ma Huang, has been used by native physicians for some 5000 years. According to this authority Ma Huang is of value as a circulatory stimulant, diaphoretic, antipyretic, sedative in cough, and it is an ingredient of many famous prescriptions.

1.6. Ephedrine and It's Uses

Derived from the Chinese plant ma huang, ephedra or better known as ephedrine, is found both naturally and synthetically in various dietary supplements, over the counter herbal stimulants, prescription cold and flu remedies, asthmatic aid products, as well as several illicit drugs. Ephedra has been used for over two thousand years to treat bronchial asthma cold and flu, chills, lack of perspiration, headache, nasal congestion, aching joints and bones, cough and wheezing and edema. In Western terms, ma-huang is considered to have diaphoretic, diuretic, central nervous system stimulating and antiasthmatic activity. The stem (herb) of ephedra contains a number of active compounds, including small amounts of an essential oil, and most important, one or two percent alkaloids composed mainly of ephedrine and pseudoephedrine, with ephedrine ranging from thirty to ninety percent depending on the source. Alone, ephedrine is a very powerful amphetamine-like compound. Thorough literature search in the field of nitroketene dithioacetal chemistry showed that there is no report that NKDA has been used as inorganic ligand. It made a new route of synthesizing transition metal complexes with Nitroketene dithioacetal as one ligand which is an organic moiety. The synthesized mixed ligand transition metal complex with drug like ephedrine is also a new novel route in Inorganic chemistry. The drug activity can be improved by changing it into new complexes. The biological activity of the drug molecules were compared with the synthesized metal complexes and found that the complexes show better antibacterial activities than the drug ephedrine. Also Central nervous system studies were carried out with synthesized complexes and found that the complexes have CNS depressant activities. Hence as a future work the complexes those were synthesized can be used as CNS depressant drugs.

MATERIALS AND METHODS:

Analar grade chemicals and reagents were used in all the synthetic steps.

Metal Salts: The metal salts used were all purchased in the pure form from Sigma Aldrich Chemicals. They include copper(II) chloride hexahydrate, iron(III) chloride hexahydrate, cobat(II) chloride hexahydrate, zinc(II) sulphate pentahydrate, iron(II) sulphate, zinc(II) chloride and nickel(II) chloride hexahydrate.

Solvents: The solvents used include: Distilled water, Ethanol, Methanol, Acetone, Chloroform, Petroleum ether, Benzene and Dimethylsulfoxide (DMSO).

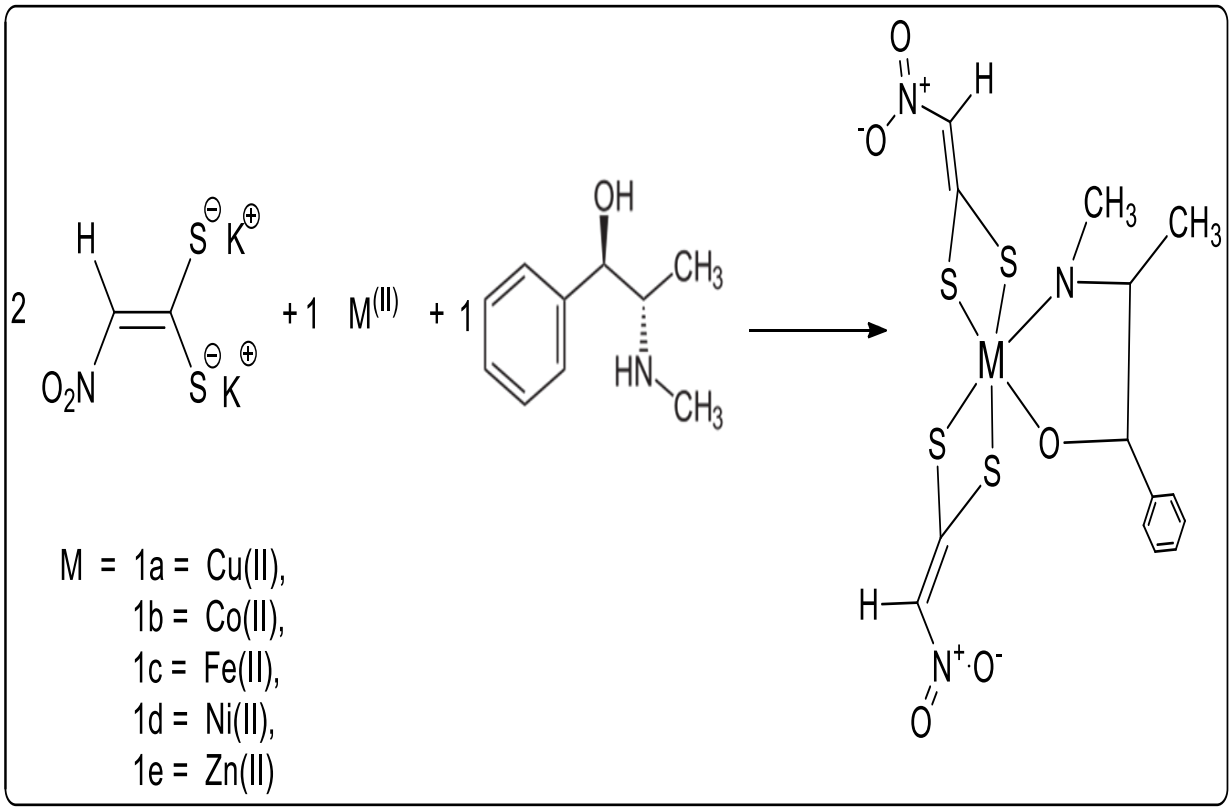
The progress of product formation was monitored by TLC using hexane and ethyl acetate solvent system. Purification of all compounds carried out by column chromatography using silica gel 100-200 mesh. Melting points were noted using IN-LAB equipment. UV and IR spectral data were recorded in Shimadzu instrument as neat and KBr pellet. ^{1}H &^{13}C NMR data were recorded in Bruker-300 MHz NMR using $CDCl_3$ as solvent. Elemental analysis data for selected compounds were collected in Thermo Finnigan-EA11112 instrument.

2.1. Experimental section

2.1.1. Synthesis of Mixed Ligand NKDA-Metal-Ephedrine Complexes 2a-2e

5 mmole of metal salts ($CuCl_2$, $ZnCl_2.4H_2O$, $NiCl_2.6H_2O$, $FeCl_3$ and $CoCl_2.6H_2O$) was dissolved in 10 ml of acetone followed by addition of 5 mmole (3.372g) of ephedrine hydrochloride and 10 mmole (1.231g) of NKDA. The mixtures were refluxed for 3 hours and left to stand overnight. The precipitate formed was filtered, washed with methanol and stored in a well-labeled container and dried over $CaCl_2$ in a dessicator.

Scheme of Synthesis of Complexes (1a-1e)



3.1. CHARACTERIZATION OF COMPLEXES

3.1.1 Solubility Test

The solubility of the complexes was studied in various solvents such as distilled water, ethanol, methanol, acetone, chloroform, benzene, dimethyl sulfoxide, petroleum ether.

3.1.2 Melting Point Test

The melting point and decomposition temperature of both the ligands and complexes were determined using the Gallenkamp apparatus at BioChemistry Department.

3.1.3 Thin Layer Chromatography

The thin layer chromatography of the metal salts, ligands and the complexes were carried out to determine their purity. This is based on variation in the rate of migration of the components sample. Thin layer chromatography was carried out by using a TLC plate coated with silica gel. The solution of the compounds in their respective solvents were made and spotted on the TLC plate. These were developed using a mixture of methanol and acetone (7:3) for the complexes. After the developments, the chromatograms were dried and viewed under UV lamp at 254 nm and 670 nm respectively, in order to determine their R_f values.

3.1.4 Conductivity Test

The molar conductance of the complexes was determined in DMSO using HANNA instrument conductivity meter, with a cell constant of 0.83.

3.1.5 UV-Visible Spectroscopy

The UV-Visible spectra of the ligands and the complexes in DMSO solution were run on the Aquamate V4.60 UV/Visible spectrophotomer, at the Chemistry Department, VHNSN College, Virudhunagar.

3.1.6 Infrared Spectroscopy

The infrared spectra were recorded using KBr pellets with Buck Scientific M500 IR spectrophotometer at the Chemistry Department, VHNSN College, Virudhunagar.

4.1. Physical Properties of mixed ligand metal complexes of NKDA and Ephedrine 1a-1e

The results of the physical properties, IR, UV-Visible spectra of some mixed NKDA- Ephedrine - metal complexes are presented in Table 1-4.

Table 1: Solubility Data of some mixed ligand NKDA-Ephedrine-Metal complexes

Ligand/ Complex	Distilled water		Ethanol		Methanol		Acetone		Chloroform		Benzene	
	C	H	C	H	C	H	C	H	C	H	C	H
NKDA	S	S	S	S	SS	SS	NS	NS	NS	NS	NS	NS
Ephedrine	S	S	S	S	SS	SS	NS	NS	NS	NS	SS	SS
Cu(eph)(NKDA)2	NS	NS	SS	SS	SS	SS	SS	SS	NS	NS	NS	NS
Co(eph)(NKDA)2	NS	NS	SS	SS	SS	SS	SS	SS	NS	NS	NS	NS
Ni(eph)(NKDA)2	NS	NS	SS	SS	SS	SS	SS	SS	NS	NS	NS	NS
Zn(eph)(NKDA)2	NS	NS	SS	SS	SS	SS	SS	SS	NS	NS	NS	NS
Fe(eph)(NKDA)2	NS	NS	SS	SS	SS	SS	SS	SS	NS	NS	NS	NS

S= soluble, SS = slightly soluble, NS = not soluble, C= cold, H= hot.

Table 2: Some physical properties of some mixed ligand NKDA-Ephedrine-Metal complexes

Ligand/ Complex	Colour	M.pt (oC)	Rf	% yield	Conductivity scm2mol-1	Molecular weight	Exact mass	Elemental Analysis					
								C	H	M	N	O	S
NKDA	Reddish	212	0.56	87.3	$1.20x10^{-6}$	216	215.78	31.3	7.23	----	4.57	10.44	20.9
Cu(eph)(NKDA)2	Blue	> 360	0.87	65.6	152.3	497.07	495.91	33.8	3.04	12.00	8.45	16.09	25.8
Co(eph)(NKDA)2	purple	> 360	0.82	55.0	100.5	492.47	491.92	34.1	3.07	11.97	8.53	16.24	6.04
Ni(eph)(NKDA)2	brown	> 360	0.90	40.1	90.8	492.23	490.92	34.2	3.07	11.92	8.54	16.25	26.1
Zn(eph)(NKDA)2	Purple	> 360	0.94	57.5	103.0	498.92	496.91	33.7	3.03	13.10	8.42	16.03	25.7
Fe(eph)(NKDA)2	Green	> 360	0.93	46.0	148.0	488.92	488.92	34.4	3.09	11.41	8.59	16.35	26.2

All the complexes are stable in air. The higher melting point of all isolated anhydrous complexes (> 360ºC) than the integral ligand (211ºC) may reflect their relative stability. All the complexes are insoluble in water, soluble to very limited extent in common organic solvents but considerable extent in dimethylformamide (DMF) and DMSO. The results of molar conductance in DMSO solutions showed that all the mixed ligand complexes are electrolytes. The high melting point confirms the formation of the mixed complexes. All the mixed ligand complexes are of various colour.

5.1. RESULTS AND DISCUSSION

5.1.1. INFRARED SPECTRA OF MIXED LIGAND NKDA – EPHEDRINE - METAL COMPLEXES

Selected IR data (cm-1) of NKDA, Ephedrine and their mixed ligand complexes are presented in Table 3.

Table 3: Selected IR data (cm^{-1}) for mixed ligand NKDA-Metal-Ephedrine complexes

Ligand/ Complex	υ C-S	υ C-H	υ C=C	υ C-NO2	υ M-S	υ N-CH=C	υ C-N (Stretch	υ N-O Stretching	υ M-O	υ M-N	υ O-H	υ C-O
NKDA	700(C-S stretch)	650 (sp2 CH bend)	1650	1390 symmetric (medium)	-----	1410	(1190–1130)1100	1170	-------	----------	----------	----------
Eph.HCL	----	------	-----		-----	------	------	-----	-----	-----	3330 (3500)	1051 (1044)
Cu(eph)(NKDA)2	1098	623	1661	1399	2380	1464	1107	1120	3666	3767	----	987
Co(eph)(NKDA)2	1113	694	1656	1517	2376	1459	1119	1513	3755	3906	----	972
Ni(eph)(NKDA)2	1110	640	1657	1537	2391	1473	1014	1118	3759	3902	----	991
Zn(eph)(NKDA)2	831	637	1657	1247	2382	1454	1129	1250	3510	3752	----	985
Fe(eph)(NKDA)2	831	703	1658	1398	2376	1509	1037	1256	3908	3748	-----	959

A comparison of the most intense band positions in the free ligand (ephedrine hydrochloride) and the formed complexes are listed in Table 3.

The IR band in the range of ~1537cm^{-1}and ~1398cm^{-1} showed the presence of nitro group(-NO_2) in the products. The presence of (C=C) was observed in the frequency range of ~1656cm^{-1}. The presence of N – CH=C band was observed in the range of 1459 cm^{-1}. The spectrum of free ligand displays a series of significant bands as: 3330, 1051cm^{-1} which may assign to υ(OH), υ(CO). The lower appearance shinned on bands of –OH and –NH groups supports of the presence of intraligand H–bonding between the two neighboring groups. This is expected due to the distribution of –OH and –NH groups, which primates this behavior as appeared from Molecular Modeling for the minimum internal energy structure (3.385 kcal/mol). The new bands assigned for υ(M-N) and υ(M-O) are easily characterized in the range 3752-3902cm^{-1} The significant spectral similarity among the bivalent metal complexes reflects the same nature of the ligand in coordination with all metal ions. The bands at 1107-1129cm^{-1} in the ephedrine-metal complexes belong to the C–H stretching.[28,29] One of the most intense band observed at 1170-1250 cm^{-1}, is a very characteristic for N-O strectching. The other intense band at 1304cm^{-1} is characteristic for O-H deformation, δ(OH) in plane. The band observed at 623 and 694 cm^{-1} for Cu(II)and Co(II) complexes, respectively, assigned to υ(CH).[30] The frequency spectral region gives important information about the nature of the metal – ligand bonds. We observed bands around ~ 3700cm^{-1} in all complexes spectra are assigned to υ (M-O)[31]and some bands were observed around 3900 cm^{-1}. Other significant band at 2376-2391 cm^{-1} may be assigned to υ (M-S).

5.1.2. UV Spectra of Mixed Ligand NKDA-Metal Ephedrine Complexes 2a-2e

Table 4: UV/Vis Spectra of NKDA – metal-Ephedrine Complexes

Ligand/ Complex	Wavelength (nm)
NKDA	324, 410
Eph.HCL	490
Cu(eph)(NKDA)2	590,645
Co(eph)(NKDA)2	580, 640
Ni(eph)(NKDA)2	655
Zn(eph)(NKDA)2	580
Fe(eph)(NKDA)2	660

Electronic spectra of complexes display very strong absorption band near 580-660 nm assigned to charge transfer band. This absorption band can be assigned to a charge transfer transition It has to be mentioned that in the visible range two absorptions are observed for Co-NKDA-Eph complex at 580 and 640 nm. With no doubts, these bands are due to the d–d transitions of the planar complex. Similarly, the square planar Eph-Ni(II)-NKDA complex obtained in the aqueous solution shows transition at 655 nm . These d–d transitions cause that the discussed compounds are brown. Copper(II) complex shows a broad absorption band at 580 nm (21739 cm-1) which can be assigned to d-d transition corresponding to 2T2g - 2Eg. As expected for a d10 electronic configuration, the electronic spectrum of zinc(II) complex does not show any d-d transition. The observed bands are due to the ligand and charge transfer transitions. The bands at 580 nm are assigned to n - Π* transition. The yellow color of the complex may be conjured as having arisen from this absorption in the visible region. Iron(III), deduced as a high spin(d5) complex based on its magnetic susceptibility, shows a very broad band around 660 nm which can be assigned to spin forbidden d-d transition as well as charge transfer transitions.

5.1.3. H^1 NMR Spectra of Mixed Ligand NKDA-Metal Ephedrine Complexes 2a-2e

^{1}H–NMR spectrum of the complexes were recorded in **DMSO** and compared with the ligand to confirm the binding of active sites towards the metal ion. The spectrum showed a multiplet in the region δ = 1.12 ppm, which has been assigned for methyl protons (CH_3 –CH-). A singlet peak in the region δ = 2.47 ppm for the other methyl protons (CH_3 –NH). Singlet peaks appeared at region δ = 3.26 and 4.73 ppm were assigned for CH proton of MeCH-NH and PhCH(OH) groups, respectively. The aromatic benzene ring protons appeared at 7.36ppm.

5.1.4. C^{13} NMR Spectra of Mixed Ligand NKDA-Metal Ephedrine Complexes 2a-2e

Similarly in ^{13}CNMR the olefinic carbon atoms were appeared in the range of ~146.1ppm for the products 2a -2e. The benzyl methylenic carbons were appeared in the range between ~128 and ~126 ppm. The olefinic quaternary carbons were appeared in the range between ~138.5ppm for the products 2a -2e. The –CH_3-CH peak appeared at in ~13 ppm. The –CH_3-NH peak appeared at in ~11 ppm.

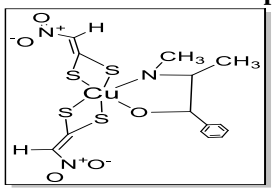
The Fab-MS M+ ion peaks and C, H, N elemental analysis data for the product 1a to 1e showed good agreement with the calculated values for the confirmation of molecular weight of the products. EDX analysis data confirmed the presence of elements and the corresponding metals in the complexes 2a-2e.

PXRD measurements were carried out to examine the phase and structure of the synthesized complexes. The PXRD pattern of the complexes shows a broad

line parallel to the amorphous nature appears at a 2θ range between 15-30°. The surface morphology of the complexes was observed by scanning electron microscopy. Figure 1A shows the different magnification of SEM images of the complexes is provided. From these images we confirmed that the synthesized complexes are in nanoparticle size.

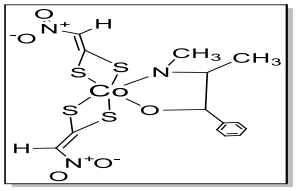
6.1. Structural characterization of products (2a – 2e)

6.1.1. Structural characterization of product 2a



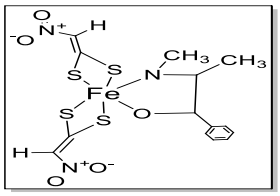
Rf = 0.87 (90:10 hexane : ethyl acetate) MP = 360-366 ˚C; Yield: 65.6% UV (methanol) λmax 590,645 nm; IR(nujol) ν 1098 **(**C-S), 623 (C-H), 1661(C=C), 1107(C-NO_2), 2380(M-S), 1464(N-CH=C), 1107(C-N Stretch), 1120(N-O Stretching), 3666(M-O), 3767(M-N), 987(C-O) cm^{-1}; ^1H NMR (300 MHz, CDCl3) δ 2.47 (s, Me-N), δ3.26(m, CH3-CH), δ4.73(d,Ph-CH-OH), δ7.36(-C_6H_5) ppm ; ^{13}C NMR (75 MHz, CDCl3) δ113.6 (olefinic-C), 146.1(quaternary =C), δ11(CH_3-N), δ13, 52(CH_3-CH), δ71(C6H5-CH) ppm.

6.1.2. Structural characterization of product 2b



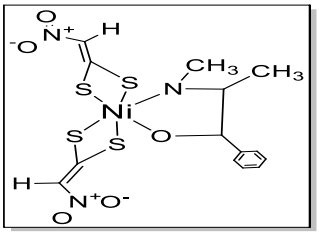
Rf = 0.82 (90:10 hexane : ethyl acetate) MP = 360-376 ˚C; Yield: 55.0% UV (methanol) λmax 580,640 nm; IR(nujol) ν 1113 **(**C-S), 694 (C-H), 1656(C=C), 1517(C-NO_2), 2396(M-S), 1459(N-CH=C), 1119(C-N Stretch), 1113(N-O Stretching), 3755(M-O), 3906(M-N), 972(C-O) cm^{-1}; ^1H NMR (300 MHz, CDCl3) δ 2.47 (s, Me-N), δ3.26(m, CH3-CH), δ4.73(d,Ph-CH-OH), δ7.36(-C_6H_5) ppm ; ^{13}C NMR (75 MHz, CDCl3) δ113.6 (olefinic-C), 146.1(quaternary =C), δ11(CH_3-N), δ13, 52(CH_3-CH), δ71(C6H5-CH) ppm.

6.1.3. Structural characterization of product 2c



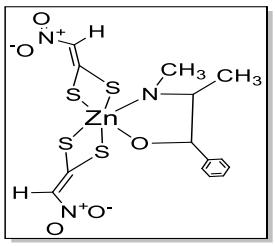
Rf = 0.93 (90:10 hexane : ethyl acetate) MP = 363-371 ˚C; Yield: 46.0% UV (methanol) λmax 660 nm; IR(nujol) ν 831 **(**C-S), 703 (C-H), 1658(C=C), 1398(C-NO_2), 2376(M-S), 1509(N-CH=C), 1037(C-N Stretch), 1256(N-O Stretching), 3908(M-O), 3748(M-N), 959(C-O) cm^{-1}; ^1H NMR (300 MHz, CDCl3) δ 2.47 (s, Me-N), δ3.26(m, CH3-CH), δ4.73(d,Ph-CH-OH), δ7.36(-C_6H_5) ppm ; ^{13}C NMR (75 MHz, CDCl3) δ113.6 (olefinic-C), 146.1(quaternary =C), δ11(CH_3-N), δ13, 52(CH_3-CH), δ71(C6H5-CH) ppm.

6.1.4. Structural characterization of product 2d



Rf = 0.90 (90:10 hexane : ethyl acetate) MP = 361-369 ˚C; Yield: 40.1% UV (methanol) λmax 655 nm; IR(nujol) ν1110 **(**C-S), 640 (C-H), 1657(C=C), 1537(C-NO_2), 2391(M-S), 1473(N-CH=C), 1014(C-N Stretch), 1118(N-O Stretching), 3759(M-O), 3902(M-N), 991(C-O) cm^{-1}; ^1H NMR (300 MHz, CDCl3) δ 2.47 (s, Me-N), δ3.26(m, CH3-CH), δ4.73(d,Ph-CH-OH), δ7.36(-C_6H_5) ppm ; ^{13}C NMR (75 MHz, CDCl3) δ113.6 (olefinic-C), 146.1(quaternary =C), δ11(CH_3-N), δ13, 52(CH_3-CH), δ71(C6H5-CH) ppm.

6.1.5. Structural characterization of product 2e



Rf = 0.94 (90:10 hexane : ethyl acetate) MP = 363-372 ˚C; Yield: 57.5% UV (methanol) λmax 580 nm; IR(nujol) ν831**(**C-S), 637(C-H), 1657(C=C), 1247(C-NO_2), 2382(M-S), 1454(N-CH=C), 1129(C-N Stretch), 1250(N-O Stretching), 3510(M-O), 3752(M-N), 985(C-O) cm^{-1}; ^1H NMR (300 MHz, CDCl3) δ 2.47 (s, Me-N), δ3.26(m, CH3-CH), δ4.73(d,Ph-CH-OH), δ7.36(-C_6H_5) ppm ; ^{13}C NMR (75 MHz, CDCl3) δ113.6 (olefinic-C), 146.1(quaternary =C), δ11(CH_3-N), δ13, 52(CH_3-CH), δ71(C6H5-CH) ppm.

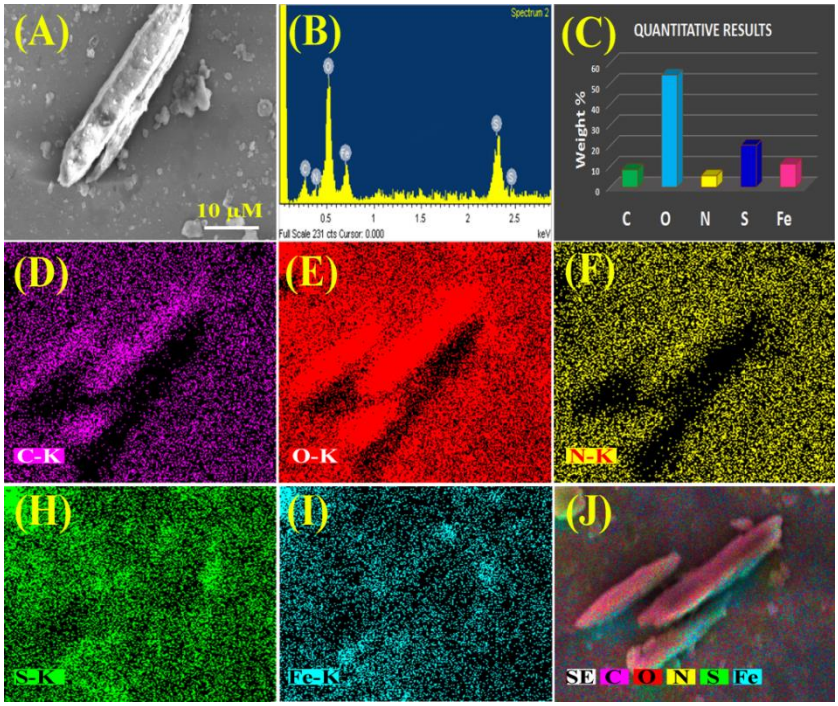


Fig. 1 (A) SEM, (B) EDX, (C) quantitative results, (D-J) elemental color mapping of EFN.

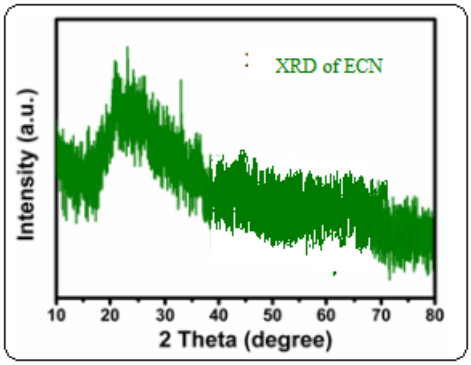


Fig.2 XRD pattern for NKDA-Metal-Eph complexes

7.1. Antibacterial activity studies of mixed ligand transition metal complexes of nitroketene dithioacetal with ephedrine

The antibacterial activity studies in nutrient agar medium for the following gram+ve and gram-ve organisms *Escherichia coli, Proteus sp, Serratiamarcescens, Pseudomonas aureginosa, Citrobactorsp, Klebsiella pneumonia, Bacillus subtills, Micrococcus, Staphylococcusaureus and Streptococcus viridians* were carried out and the results were tabulated in Table – I. From the results it is found and reported that all the new metal complexes with NKDA motif were exhibiting anti bacterial activity in the form of zone of inhibition.

Table I : Antibacterial activity of NKDA – Metal – Ephedrine complexes 2a-2e

Name of the Culture	Zone of Inhibition in mm for Products (2a-2e)					Standard
	2a	2b	2c	2d	2e	Sulfadiazine
Escherichia coli	**16**	15	**15**	**18**	11	22
Proteus sp.	**15**	10	**14**	**16**	14	17
Serratiamarcescens	**17**	13	**17**	**15**	9	21
Pseudomonas aeruginosa	**18**	16	**18**	**16**	15	23
Citrobactor sp.	**14**	9	**15**	**15**	11	20
Klebsiella pneumonia	**13**	11	**18**	**16**	14	19
Bacillus subtilis	18	**22**	11	16	**22**	25
Micrococcus	15	**23**	13	21	**16**	24
Staphylococcus aureus	22	**17**	21	22	**20**	30
Streptococcus viridans	21	**20**	18	20	**17**	28

From the measured results in the form of zone of inhibition in mm, it is found and reported that the complex 2d showed potent antibacterial activity against gram-ve *Escherichia coli* bacterial strains compare to the standard drug sulphadiazine. The complexes 2a, 2c showed potent antibacterial activity against gram-ve *Pseudomonas aeruginosa* bacterial strains compare to the standard drug sulfadiazine. The complexes 2a, 2c, 2d, 2e, showed potent antibacterial activity against gram+ve *Staphylococcus aureus* bacterial strains compare to the standard drug sulfadiazine. The complex 2c showed moderate antibacterial activity against gram+ve bacterial strains compare to the standard drug sulfadiazine.

8.1. Central Nervous System activity studies of mixed ligand transition metal complexes of nitroketene dithioacetal with ephedrine

Animals used

Albino mice of both sexes of weight ranges between 25g and 45g were used for CNS depressant activity study. The animals were kept in torsion polypropylene cages in a room maintained under controlled atmospheric conditions. The animals were fed with standard diet and kept in dark/light cycle 12hrs/12hrs and drinking water ad libitum.

Preparation of dose and Route of Administration

The dose concentration of 10mg of all the new complexes 1a-1e, 2a-2e and 3a-3e, 5mL of distilled water and 2 mg of carboxymethyl cellulose (CMC) powder was weighed and taken in a morter and pestle. The mixture was triturated well to convert the solution as a gel. From this bulk gel, doses for individual animal was taken based upon the animal body weight and fed to the animal orally using an oral canal.

Experimental measurement of locomotor activity of animals in Actophotometer

The animals were divided into 7 groups. Six animals were taken in each group (n= 6). Each albino mice was weighed in a physical balance and marked individually. Initially all the animals were placed in the Digital actophotometer activity cage (Size of 36 x 37cm) for 10 minutes to determine the basal locomotor activity score. Animals of Group–1 are served as control and treated with 2mg of carboxy methyl cellulose in 5mL of distilled water. Animals of Group-2 were orally treated with the standard drug Chlorpromazine 3mg/kg, (i.p.) using a oral canal. Animals in between Group-3 and Group-7 were orally treated with the new 5 complexes based on the animal body weight in the form of well triturated gel prepared using 5mL of distilled water, 10mg of complexes 2a-2e and 2mg of carboxy methyl cellulose. All the animals were left freely in the animal cage for 30 minutes for the absorption of drugs. The locomotor activity score for all the animals were again determined for all the 7 Group animals after the drug absorption. The percentage of CNS depressant activity was calculated using the formula

$$\% \text{ of CNS depressant activity} = \frac{A - B}{A}$$

A = locomotor activity score before drug treatment

B = locomotor activity score after drug treatment

The Mean change in locomotor activity score recorded for each group of animals were calculated and the values are given in the table between Table – 1 and Table - 7.

Table – 1 - Locomotoractivity study of Control – (Group-1)					
S.No	**Animal body Weight (g)**	**Dose (mg/mL)- Control**	**Locomotor activity score in 10 minute**		**% of depressant activity***
			Before treatment	**After treatment**	
1	38	2mg of CMC / 5ml of distilled water	175	171	2.29
2	40		124	118	4.83
3	37		202	198	1.98
4	29		220	214	2.73
5	27		224	219	2.23
6	32		157	152	3.18
Mean =			**183.67**	**178.67**	**2.87**

Table – 2 -Locomotor activity study of chlorpromazine (standard) – (Group-2)					
S.No	**Animal body Weight (g)**	**Dose (mg/mL)- chlorpromazine**	**Locomotor activity score in 10 minute**		**% of depressant activity**
			Before treatment	**After treatment**	
1	36	3mg of drug/ 5ml of distilled water	124	48	61.29
2	34		174	62	64.37
3	37		302	98	67.54
4	28		220	72	67.27
5	31		224	83	62.94
6	30		298	112	62.42
		Mean =	**223.83**	**79.16**	**64.30**

Table – 3 - Locomotor activity study of product – 2a – (Group-3)					
S. No	**Animal body Weight (g)**	**Dose (mg/mL)- 2a**	**Locomotor activity score in 10 minute**		**% of depressant activity**
			Before treatment	**After treatment**	
1	23	10 mg of drug / 5ml of distilled water	169	83	50.88
2	34		148	74	50.00
3	40		298	153	48.65
4	26		276	135	51.08
5	29		178	90	49.43
6	33		231	112	51.51
		Mean =	**216.66**	**107.83**	**50.25**

Table –4 - Locomotor activity study of product – 2b – (Group-4)					
S. No	**Animal body Weight (g)**	**Dose (mg/mL)- 2b**	**Locomotor activity score in 10 minute**		**% of depressant activity**
			Before treatment	**After treatment**	
1	33	10 mg of drug / 5ml of distilled water	189	98	48.15
2	29		148	83	43.92
3	28		288	160	44.44
4	35		166	85	48.8
5	40		298	153	48.66
6	32		224	124	44.64
Mean =			**218.83**	**117.17**	**46.43**

Table – 5 - Locomotor activity study of product – 2c – (Group-5)					
S. No	**Animal body Weight (g)**	**Dose (mg/mL)- 2c**	**Locomotor activity score in 10 minute**		**% of depressant activity**
			Before treatment	**After treatment**	
1	40	10 mg of drug / 5ml of distilled water	165	96	41.81
2	33		142	77	45.77
3	28		312	185	40.71
4	24		271	147	45.76
5	27		223	131	41.26
6	36		186	99	46.77
Mean =			**216.5**	**122.5**	**43.68**

Table – 6 - Locomotor activity study of product – 2d – (Group-6)					
S. No	**Animal body Weight (g)**	**Dose (mg/mL)- 2d**	**Locomotor activity score in 10 minute**		**% of depressant activity**
			Before treatment	**After treatment**	
1	29	10 mg of drug / 5ml of distilled water	276	132	52.17
2	38		178	83	53.37
3	21		272	137	49.63
4	31		232	108	53.44
5	26		212	104	50.94
6	36		165	79	52.12
Mean =			**222.5**	**107.16**	**51.95**

Table – 7 - Locomotor activity study of product – 2e – (Group-7)					
S. No	Animal body Weight (g)	Dose (mg/mL)- 2e	Locomotor activity score in 10 minute		% of depressant activity
			Before treatment	After treatment	
1	35	10 mg of drug / 5ml of distilled water	189	84	41.81
2	26		324	147	45.77
3	39		268	129	40.71
4	29		267	120	45.76
5	31		198	90	41.26
6	34		287	128	46.77
Mean =			**255.5**	**116.33**	**54.5**

Table – 8: Cumulative Locomotor Activity Results Complexes 2a – 2e				
Product number	Dose	Locomotor activity score for 10 minutes		% of CNS depressant activity
		Before treatment	After treatment	
Control	**2mg cmc / 5mL H_2O**	**183.67±39.06^{a}**	**178.67±39.24^{a}**	**2.87±1.04^{d}**
Chlorpromazine	**3mg**	**223.67±69.39^{a}**	**79.16±23.51^{b}**	**64.30±2.59^{i,j}**
2a	**10mg**	**216.66±64.92^{a}**	**107.83±13.86^{c}**	**50.25±6.32^{f}**
2b	**10mg**	**218.83±62.89^{a}**	**117.17±33.86^{c}**	**46.43±2.32^{f}**
2c	**10mg**	**216.50±65.22^{a}**	**122.5±39.75^{c}**	**43.68±2.69^{f}**
2d	**10mg**	**222.5±53.39^{a}**	**107.16±14.16^{c}**	**51.95±1.98^{g}**
2e	**10mg**	**255.5±72.23^{a}**	**116.33±28.86^{c}**	**54.5±2.65^{g}**

The Cumulative locomotor activity results of complexes 2a-2e were calculated and the results were tabulated in **Table – 8.** The percentages of CNS depressant activity of new complexes were compared with standard drug chlorpromazine and the results were statistically analyzed using Statistical Package for the Social Sciences (SPSS 12.0). The data were analysed with ANOVA and Duncan's multiple range test (DMRT). The data are expressed as mean±SD, for 6 animals in each group. From the results it is found and reported that all the new complexes 2a-2e are exhibiting CNS depressant activity. Among the five new complexes The products 2a, 2d, 2e showed moderate significant CNS depressant activity compare to the standard drug chlorpromazine. The products 2b and 2c showed poor significant CNS depressant activity compare to the standard drug chlorpromazine. The complex 1c exhibited the maximum percentage of CNS depressant activity of 73.65among all the other products and the complex 1e exhibited poor CNS depressant activity of 31.85 percentages among all the new products.

9.1. CONCLUSION:

We have reported the synthesis of five new mixed ligand complexes 2a-2e of NKDA motif with transition metals and drug Ephedrine. The structure of the library of products 2a-2e was characterized using UV, IR, ^{1}HNMR, ^{13}CNMR, C,H,N elemental analysis, XRD, EDX and Fab mass spectral evidences. We have reported the results of antibacterial study of new synthesized metal complexes 2a-2e with NKDA motif. In future this group of complexes with nitroketene dithioacetal motif may be used as good therapeutic drugs against

bacterial borne diseases in mankind. We have reported the central nervous system depressant activity study of nineteen newly synthesized mixed ligand transition metal complexes 2a-2e with NKDA motif using Albino mice animal screening experiment and the results were analysed with ANOVA and Duncan's multiple range test (DMRT) using SPSS.12 version. The data are expressed as mean±SD, for 6 animals in each group. The results were compared with the standard drug chlorpromazine. Among the five new complexes.The products 2a, 2d, 2e, showed moderate significant CNS depressant activity compare to the standard drug chlorpromazine. The products 2b and 2c showed poor significant CNS depressant activity compare to the standard drug chlorpromazine.

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