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SYNTHESIS AND STRUCTURAL DETERMINATION OF NOVEL CURCUMIN OXIME GOLD(III)COMPLEX:POTENTIAL CHEMOPREVENTIVE DRUG

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ABSTRACT

Cancer is a dreadful disease and any practical solution in combating this disease is of paramount importance to public health. Cancer patients have burdened by drug induced toxic side effects, and no turned to seek help from the complementary and alternative medicine hoping for a better cure. Cancer is a class of diseases characterized by out-of-control cell growth. Cancer harms the body when damaged cells divide into uncontrollably to form lumps or masses of tissue called tumors. Tumors that stay in one spot and demonstrate limited growth are generally considered to be benign. Cancerous cell manages to move throughout the body using the blood systems, destroying healthy tissue in a process called invasion. Cur cumin is a natural polyphenol. It is highly potential molecule capable of preventing and treating various cancers. The anticancer potential of cur cumin is severely affected by its limited systemic and target tissue bioavailability and rapid metabolism. Various dietary chemo preventive agents, turmeric powder or its extract are broadly used as therapeutic preparations in Indian System of medicine. In the present research work, we provide a summarized synthesis and structural determination of Curcumin Oxime derivative of Gold(III)complex. The use of these analogs for prevention of cancer tumor progression and treatments of human malignancies.

KEYWORDS: Curcumin, Curcumin Oxime, chemoprevention, therapy, human malignancy.

INTRODUCTION

The herbal traditional medicinal plants are important raw material to synthesis the phytochemicals.[1] The phytochemical, curcumin is one of the major dietary flavonoid, belonging to a group of flavonol.[2] Flavonoids have a long history of use in traditional medicines in many cultures.[3] Research in recent years has focused on several possible helpful effects of curcumin, including its potential role in preventing cancer. Recent studies suggest that curcumin can slow the growth of cancer cells because they have anti-tumor and anti-oxidant properties.[4]

Curcumin and its analogs, we would like to provide a brief survey on phytochemicals in general because phytochemicals are becoming the novel backbone of medicinal chemistry and having broad variety of biologically active compounds produced by plants such as β-carotene, ascorbic acid, folic acid, vitamin E and many others that possess either antioxidant capable of scavenging out certain reactive oxygen radicals or anti-toxicity actions. Several dietary phytochemicals are recommended for prevention of carcinogenesis. Aggarwal *et al.* have recently reviewed the cell signaling pathways in cancers that are disrupted by agents isolated from natural origins curcumin. Curcumin is a simple symmetrical β-diketone and incorporates several functional groups. The two aromatic rings containing phenolic groups are connected by two α, β-unsaturated carbonyl groups.

A large number **of** oximes have been evaluated for their anti-malarial and anti-tumor activities, because of their useful chemotherapeutic properties. In cancer treatment it has been shown that the metal chelates are more potent than the chelating agents. Metal complexes of Gold containing nitrogen and oxygen donor ligands is found to be effective catalysts for oxidation, reduction, hydrolysis and other organic transformation.[5] The red ox properties of the curcumin derivatives has been found to block cell cycle progression in a variety of malignant cell lines including those derived from the prostrate, brain, breast, pancreas and colon. These derivatives are involving as agent blocking carcinogenesis induced by heterocyclic amines.[6]

These carbonyl groups form a diketone which exists in keto- and enol- tautomeric forms where energetically more stable enol form. Curcumin exists in the keto form in acidic and neutral pH media and in the enol form in alkaline pH medium. A stable crystalline form of curcumin.

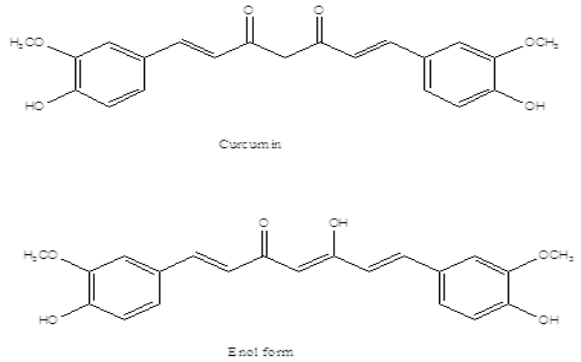


Figure: 1.

Chemicals and reagents

All chemicals were A.R. and used without further purification. All the reagents used in the preparation of ligands and their metal complexes were of reagent grade (Merck). The solvents used for the synthesis of ligands and metal complexes were distilled before use. All other chemicals were of AR grade and used without further purification.

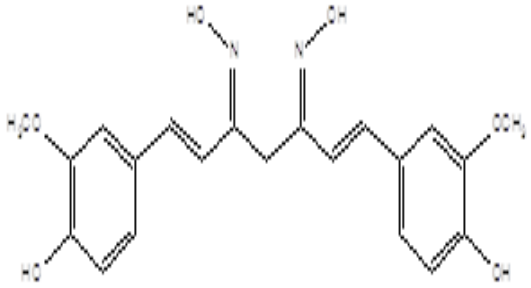
Elemental Analysis

The elemental analysis was performed by using micro analytical techniques. The I:R spectra were recorded in the range 4000-200 cm-1 using KBr discs with Perkin-Elmer model 1430 and 337. The electrical conductivity measurements were made in DMF (10-3M) at room temperature(27_+2^{o}C) using a Digisun digital conductivity meter.

The NMR spectra was recorded in DMSO-d6 on NMR spectrophotometer model JEOL Ex-90FT using TMS as the reference. The magnetic susceptibilities were determined at room temperature, on a Guoy balance using Mercury Tetrathiocyanato Cobalt(II) as a magnetic standard. Molecular weights of the complexes were determined by cryoscopy method using camphor as solvent. Magnetic measurements were carredout in the polycrystalline state on a PAR model ISSfifi vibrating sample magnetometer operating at field strength of 2-1.0 kg. High purity nickel metal was used as a standard.

Methodology: Synthesis of Ligands

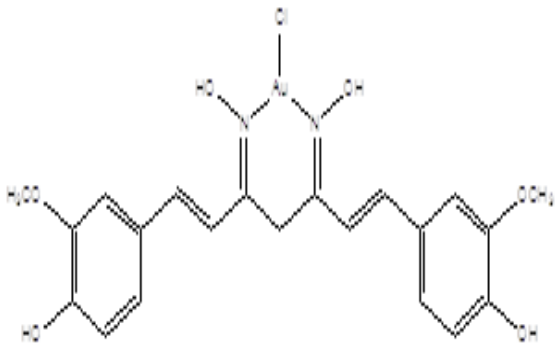
A 5 X10^{-2} $_{M}$ solution prepared by dissolving appropriate amounts of hydroxyl amine in 50 ml. methanol and 2 ml. of glycial acetic acid was added drop wise to a 5 X10^{-2} M Solution of curcumin in 50 ml. methanol while stirring and refluxed for 2 hour and the product that separated was recrystallized in methanol. Identification of the product was based on elemental analysis viz., FT-IR, HNMR, Mass Spectroscopy, ESR etc.,



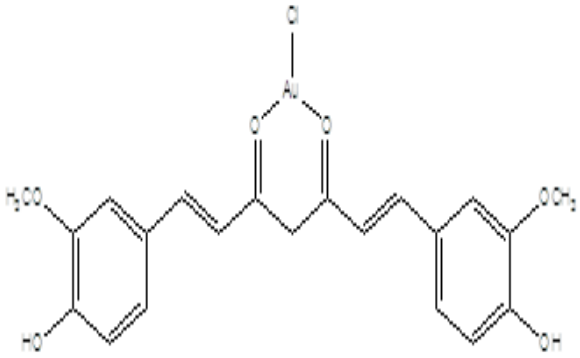
Structure of curcumin oxime(ligand) fig.2.

Synthesis of metal complexes

To 30 ml. of Gold(III) solution(5X10^{-2}M) in methanol was added (5x10^{-2} M) curcumin oxime/curcumin in methanol and 2 ml. of glycial acetic acid was added drop wise to the mixture refluxed for about one hour in a separate reflux arrangement. The solid(orange) that separated was filtered and washed with water and recrystallized with methanol.



Structure of curcumin oxime gold(III)complex fig.3.



Structure of curcumin gold(III)complex fig.4.

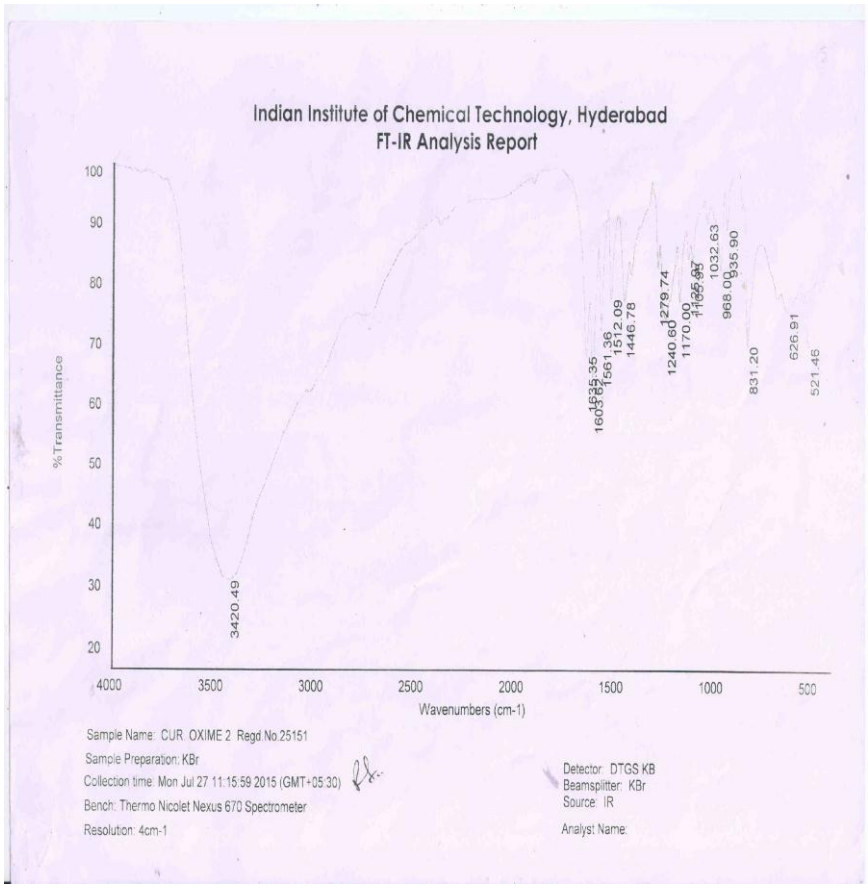
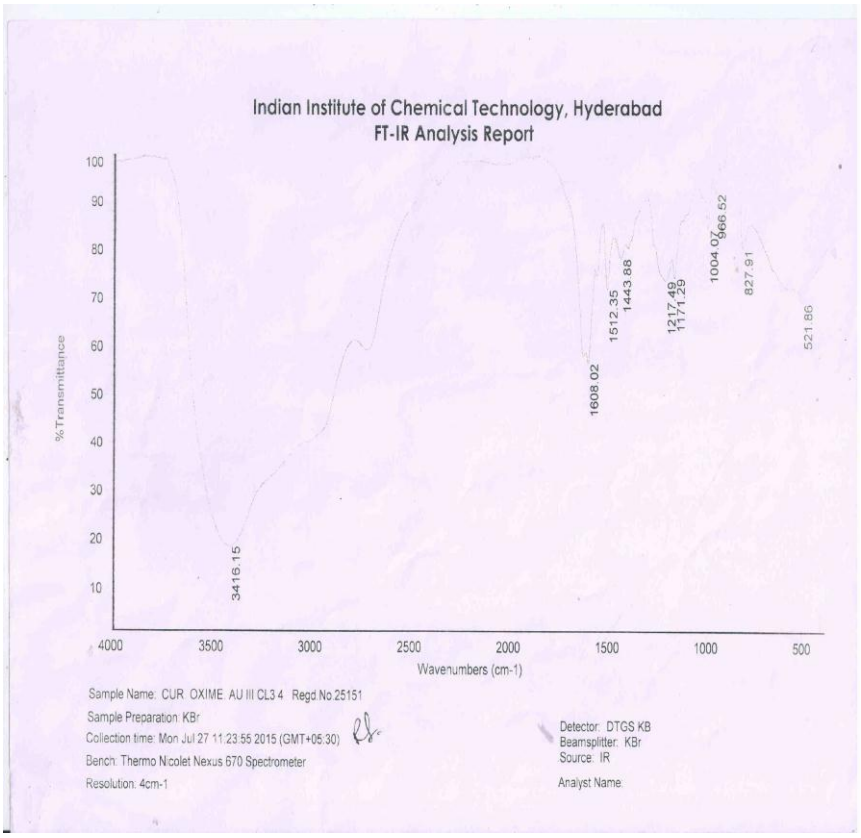

Indian Institute of Chemical Technology, Hyderabad
FT-IR Analysis Report
% Transmittance
Wavenumbers (cm-1)
3420.49
1635.35
1603.67
1561.36
1512.09
1446.78
1279.74
1240.60
1170.00
1032.63
968.00
935.90
831.20
626.91
521.46
Sample Name: CUR. OXIME 2 Regd.No.25151
Sample Preparation: KBr
Collection time: Mon Jul 27 11:15:59 2015 (GMT+05:30)
Bench: Thermo Nicolet Nexus 670 Spectrometer
Resolution: 4cm-1
Detector: DTGS KB
Beamsplitter: KBr
Source: IR
Analyst Name:

fig.5.


Indian Institute of Chemical Technology, Hyderabad
FT-IR Analysis Report
% Transmittance
Wavenumbers (cm-1)
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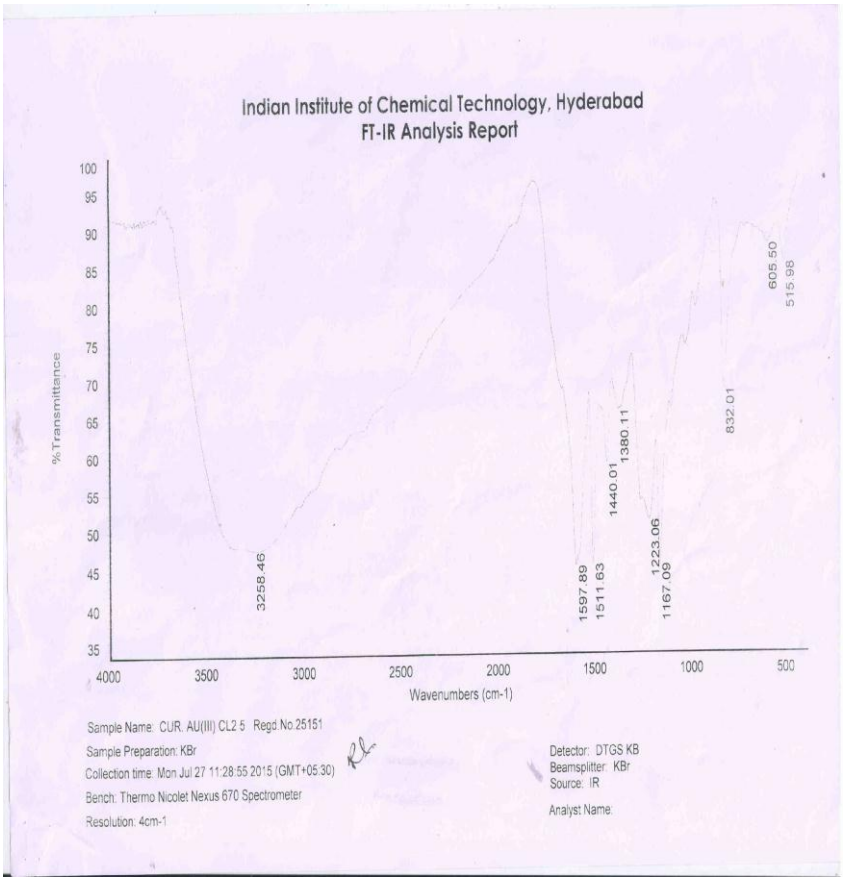
1608.02
1512.35
1443.88
1217.49
1171.29
1004.07
966.52
827.91
521.86
Sample Name: CUR. OXIME. AU III CL3 4 Regd.No.25151
Sample Preparation: KBr
Collection time: Mon Jul 27 11:23:55 2015 (GMT+05:30)
Bench: Thermo Nicolet Nexus 670 Spectrometer
Resolution: 4cm-1
Detector: DTGS KB
Beamsplitter: KBr
Source: IR
Analyst Name:

fig.6.


Indian Institute of Chemical Technology, Hyderabad
FT-IR Analysis Report
%Transmittance
Wavenumbers (cm-1)
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1440.01
1380.11
1223.06
1167.09
832.01
605.50
515.98
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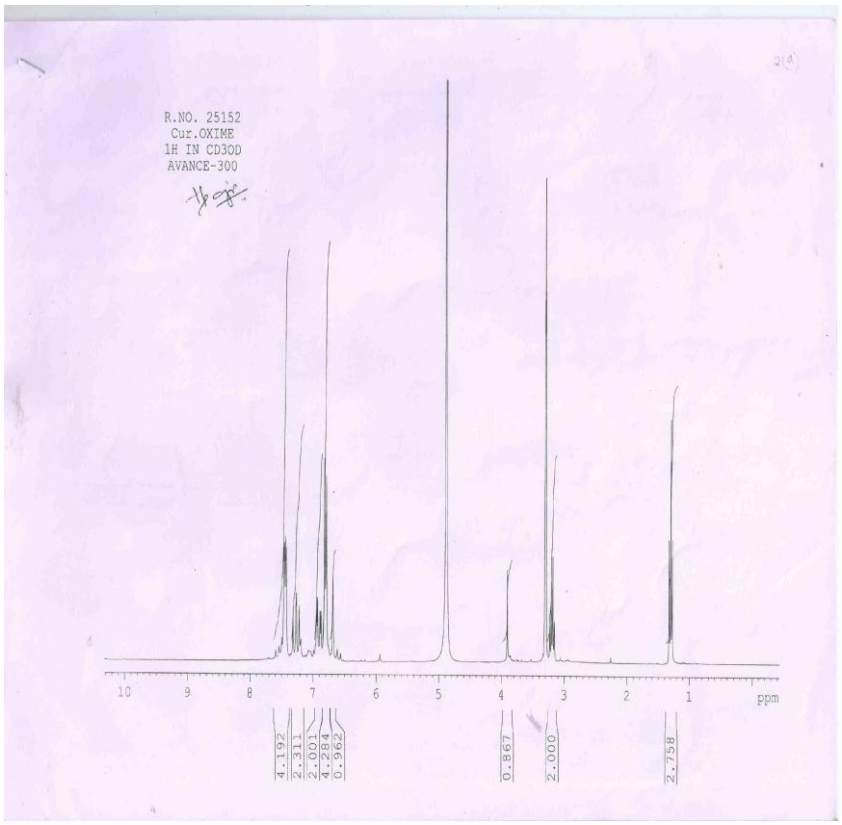
Sample Preparation: KBr
Collection time: Mon Jul 27 11:28:55 2015 (GMT+05:30)
Bench: Thermo Nicolet Nexus 670 Spectrometer
Resolution: 4cm-1
Detector: DTGS KB
Beamsplitter: KBr
Source: IR
Analyst Name:

fig.7.


R.NO. 25152
Cur.OXIME
1H IN CD3OD
AVANCE-300
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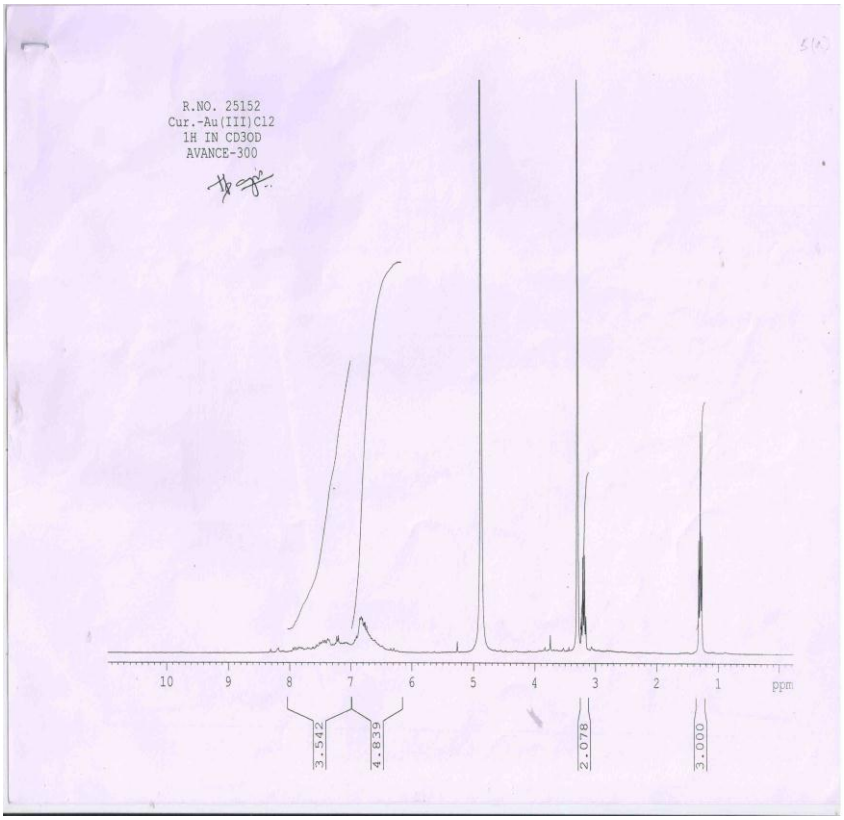
2.001
4.284
0.962
0.867
2.000
2.758

fig.8.


R.NO. 25152
Cur.-Au(III)Cl2
1H IN CD3OD
AVANCE-300
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9
8
7
6
5
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3
2
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ppm
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4.839
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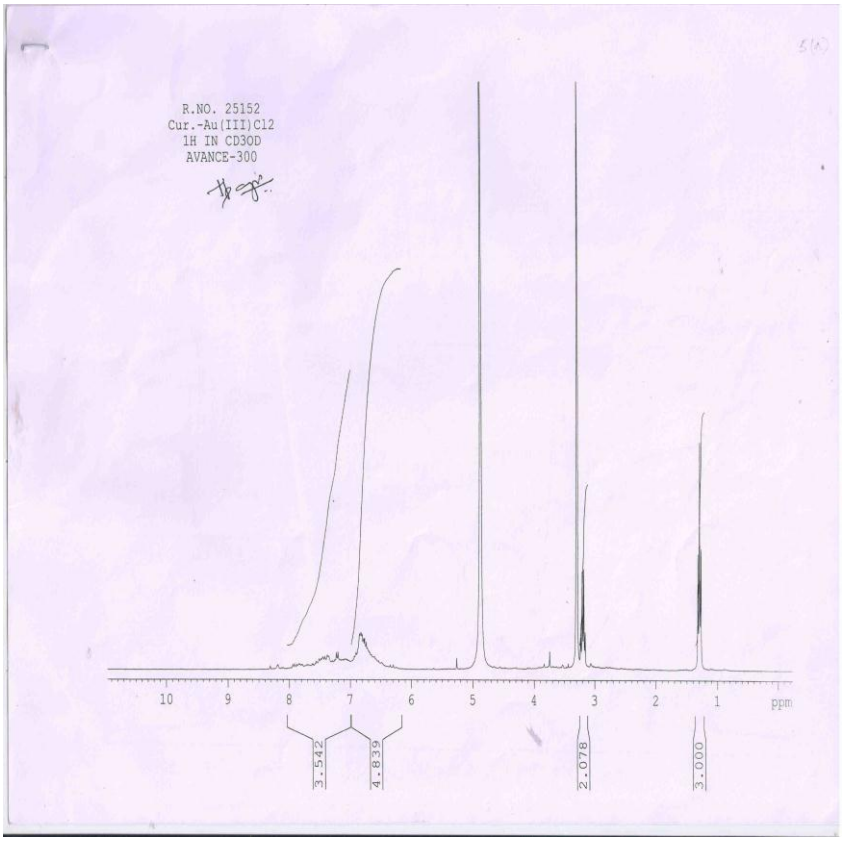
3.000

Fig: 9.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10
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8
7
6
5
4
3
2
1
ppm
3.542
4.839
2.078
3.000

fig.10.

mass spectrum.

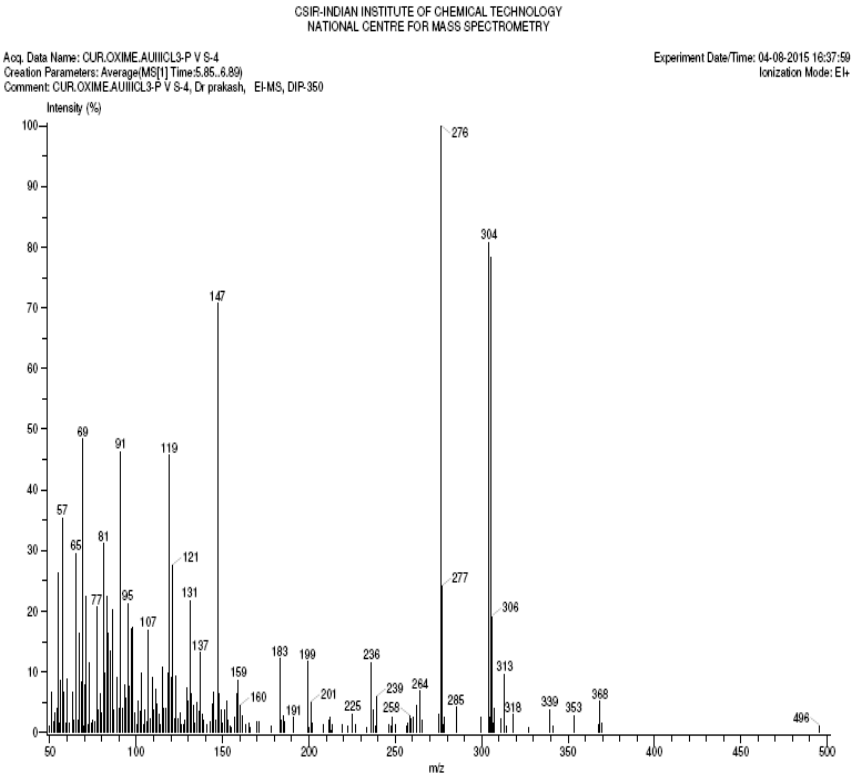

Fig. 11.

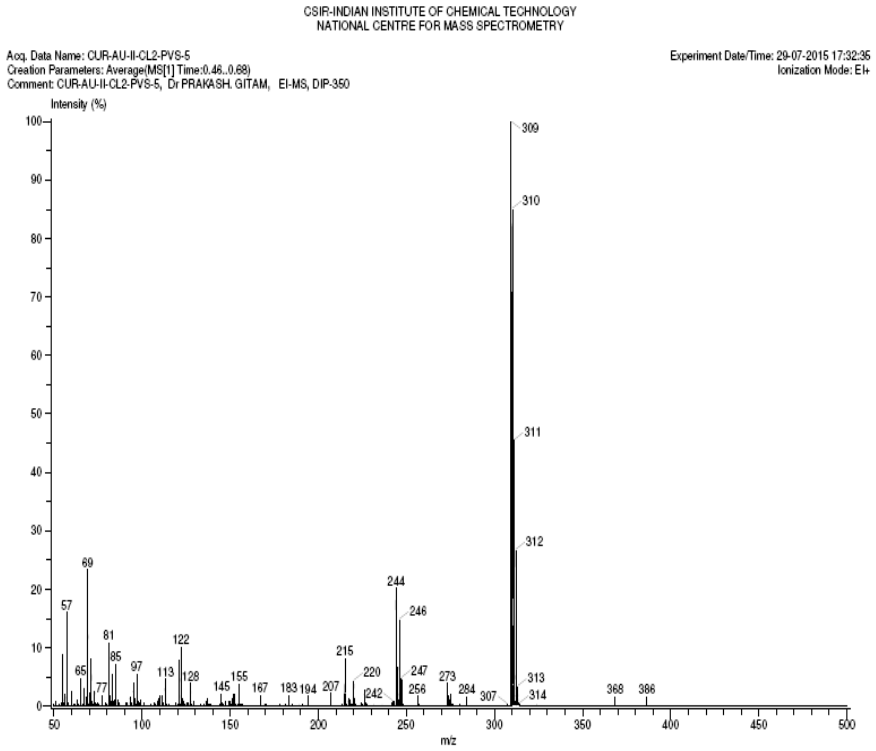

Fig. 12.

RESULTS AND DISCUSSION

The **compound was characterized using IR, ^{1}HNMR, and Mass spectrophotometric techniques. From the analysis the compound was identified.**

Curcumin oxime: From fig.5,8

IR Spectra: IR: 3420.49(labile e), 1635.35(c=o), 1603.62 & 1561.36(aromatic), 1240.60(c=o), 831.20 cm^{-1} (ligand). **HNMR**: 1.2 – 1.4(t,3H), 3.2 – 3.4(q,2H), 3.9(s,1H), 6.6 – 7.0(m,7H), 7.2 – 7.3(m,2H), 7.4 – 7.5(dd,4H). These suggest the curcumin oxime(ligand)

Curcumin gold(III)chloride: From fig.7,9

IR: 3258.46(labile e), 1597.89 & 1511.63(aromatic), 1223.06(c=o), 1167.09(c=o), 832.01 cm^{-1} (metal complex). ^{1}**HNMR:** 1.2 – 1.4(t, 3H), 3.1 – 3.3(q,2H), 6.2 – 7.0(m,5H), 7.0 – 8.0(m,4H).
These suggest the curcumin gold complex.

Curcumin oxime gold (III)chloride: From fig.6

IR Spectra: 3416.15(labile e), 1608.02 & 1512.35(aromatic), 1217.49 & 1171.29(c=o), 521.86 cm^{-1}(metal complex). **HNMR Spectra: 1.3(t,3H), 3.2(q,2H), 3.5 – 4.0 (br, 1H), 6.7(s, 1H), 6.8 (d, 5H), 6.8 – 7.0(dd,3H), 7.2 – 7.4(t,3H), 7.5(dd,5H). These suggest the Cur. Oxime gold complex.**

Mass spectra

276, base peak (removal of 2 –OCH $_3$ and 2 –OH): **304**, by removal of four "O" atoms got this peak and **368**, indicates the curcumin. From fig. 11 & 12.

The interaction of $AuCl_3$ with ligand yields compounds having composition. All complexes are found to be diamagnetic at 312 K indicating essentially a planar geometry for these compounds.

The IR spectra of ligand are characterized by the presence of a single strong band at 1635 cm^{-1} due to the central carbonyl absorptions functionalities which are equivalent. The generation of the oxime functionality at one of the carbonyls can be ascertained from the presence of band at 1561 cm^{-1} and strong carbonyl absorption at 1512 cm^{-1}. On metal complexation both the bands are shifted to lower frequency indicating their involvement in gold complexation. The introduction of oxime functionalities in the curcumin nucleus is best diagnosed from the symmetric and asymmetric bands near the 3416 cm^{-1}.

ESR Spectral analysis

Electronic Spin Resonance spectra of Gold(III)complex was recorded in DMF at liquid nitrogen temperature value equal to 26.

Magnetic studies

The magnetic moments of metal complexes were found to be subnormal, which may be attributed to the presence of magnetically coupled metal centres in dimeric complexes.

BIOLOGICAL ACTIVITY

The nuclease activity of present ligand and their complexes has been investigated on pBR 322 plasmid DNA by agarose gel electrophoreses in the presence of H_2O_2. At micro molar concentration, the ligands exhibit no significant activity in absence and in the presence of the oxidant. The nuclease activity was greatly enhanced by incorporation of metal ions and the ligands. All complexes shows much enhanced nuclease activity in the presence of oxidant, which may be due to free radical reaction with DNA.

CONCLUSION

We have synthesized the curcumin/curcumin oxime gold(III)complexes. All complexes plausible structures were supported by LSI mass spectral data along with physico-chemical and IR, HNMR, MASS, ESR spectral data. The ligands and their complexes would be screened for their anti-cancer activity against certain cancer cell lines. We have developed a simple, convenient and effective method for the synthesis of complexes. To our knowledge, this is the first report of an efficient general method for the synthesis of different gold complexes of curcumin.

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