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SYNTHESIS, STRUCTURE AND BIOLOGICAL ACTIVITY OF NOVEL CURCUMIN THIOSEMICARBOZONE GOLD(III) COMPLEX: POTENTIAL ANTICANCER DRUG

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ABSTRACT

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. 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 curcumin are broadly used as therapeutic preparations in Indian System of medicine. Cur cumin is a natural polyphenol. It is highly potential molecule capable of preventing and treating various cancers. In the present research work, we provide a summarized synthesis and biological activity of curcumin/curcumin thiosemicarbozone (curTSC) derivatives of Gold(III)complex. The use of these analogs for prevention of cancer tumor progression and treatments of human malignancies.

KEYWORDS: Curcumin, CurTSC, anticancer, therapeutic, human malignancy.

INTRODUCTION

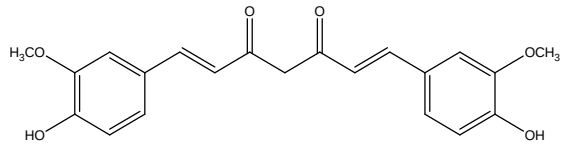
The herbal traditional medicinal plants are important raw material to synthesis the phytochemicals.[1] The phytochemical, curcumin is one of the major dietary flavonoid, belonging to a group of flavonol.[2] Flavonoids have a long history of use in traditional medicines in many cultures.[3] Research in 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]

A large number of thiosemicarbazones 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 redox 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]

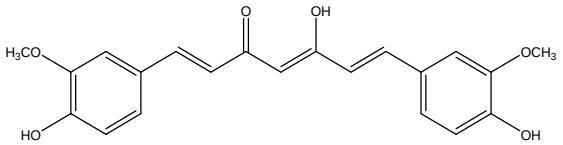
Curcumin and its analogs, we would like to provide a brief survey on phytochemical in general because phytochemicals are becoming the novel backbone of medicinal chemistry. The term "phytochemicals" refers to a broad variety of biologically active compounds produced by plants such as β-carotene, ascorbic acid, folic acid, vitamin E and many others that possess either antioxidant capable of scavenging out certain reactive oxygen radicals.

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.

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.



Curcumin



Enol form

Fig. 1a & fig1b

Arbiser *et al*. have reported Curcumin analogs without the conjugated double bond which do not exhibit any cytotoxic effects against breast cancer cells indicating the importance of conjugated double bond for anti-cancer activity of the analogs. Curcumin compounds alone or in combination with other anticancer drugs have been reported to inhibit the clonogenicity of cancer cells and induce anti-proliferative and apoptotic effects on drug resistant and sphere-forming cancer cells expressing stem cell-like markers as well as reverse the chemo resistance. Thereby they improve the cytotoxic effects induced by diverse chemotherapeutic drugs on these immature cancer cells. The molecule is stabilized by the formation of intermolecular hydrogen bonding between the enolate hydroxyl group and the ketonic carbonyl.

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

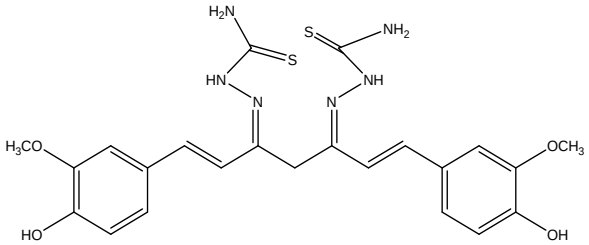
The elemental analysis was performed by using micro analytical techniques. The I:R spectra were recorded in the range 4000-200 Cm^{-1} using KBr discs with Perkin-Elmer model 1430 and 337. The electrical conductivity measurements were made in DMF(10^{-3} M) at room temperature (27_+2^{o}C) using a Digisun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



Curcumin thiosemicarbazone(CTSC):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/curcumin thiosemicarbazone 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.

RESULTS AND DISCUSSION

The compound was obtained as a crystalline orange solid. The compound isolated was characterized by using IR(fig.2), and HNMR(fig.3) spectrophotometer techniques.

From the analysis, the compound was identified as Cur.TSC.

(i) IR: 3133.26(labile e), 2064.88(C=N), 1600.13, 1510.77(Aromatic), 1442.12(C-H), 1137.65cm^{-1} (C=O)
HNMR: 7.4 – 7.7(m,5H), 7.1 – 7.2(d,1H), 6.7 – 6.9(m,6H), 6.5 – 6.6(d,1H), 5.9(bs,1H), 3.9(s,1H), 3.2(q,2H),1.3(t,2H) from fig.2a,3a.

(ii) From the analysis, the compound was identified as Cur.Au(III)complex.
IR: 3258.46(labile e), 1597.89and 1511.63(Aromatic), 1223.06 and 1167.09(C=O), 832.01 cm^{-1} (Metal ligand).
HNMR: 6.2 – 7.5(b,8H), 3.2(q,2H), 1.3(t,3H) from fig.2b,3b

(iii) From the analysis, the compound was identified as Cur.TSC.Au(III)complex.
IR: 3382.27(labile e), 1638.23, 1602.68 and 1511.98(Aromatic), 1243.52 cm^{-1} (C=O) from fig.2c,3c
HNMR: 7.2 – 7.6(6H), 6.6 – 7.1(8H), 3.4(OCH_3,6H), 3.7 – 3.9(bs,3H), 3.0 – 3.2(d,2H)

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. 4 & 5.

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 1600 cm^{-1} due to the central carbonyl absorptions functionalities which are equivalent. The generation of the thiosemicarbazone functionality at one of the carbonyl can be ascertained from the presence of band at 1510 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 3382 cm^{-1}.

All the metal complexes are stable at room temperature non hygroscopic, sparingly soluble in methanol or ethanol. The analytical data for ligand and metal chelates are consistent with their proposed molecular structure.

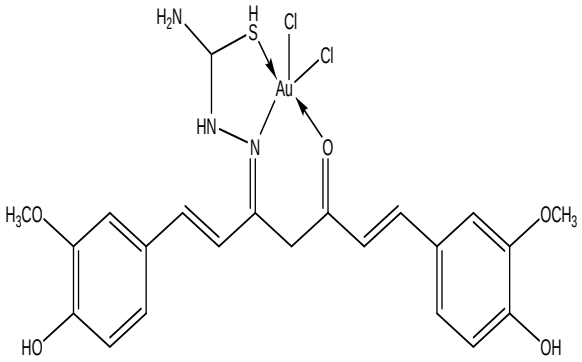


Fig.3 structure of Curcumin thiosemicarbazone Gold(III)complex;

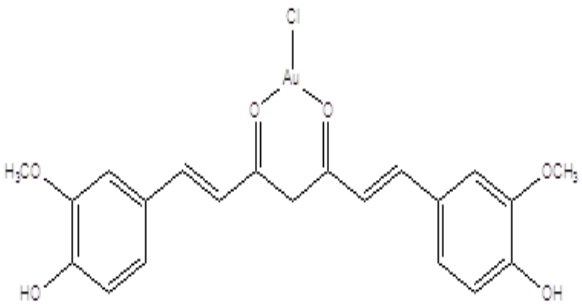


Fig. 4 structure of Curcumin Gold(III)complex

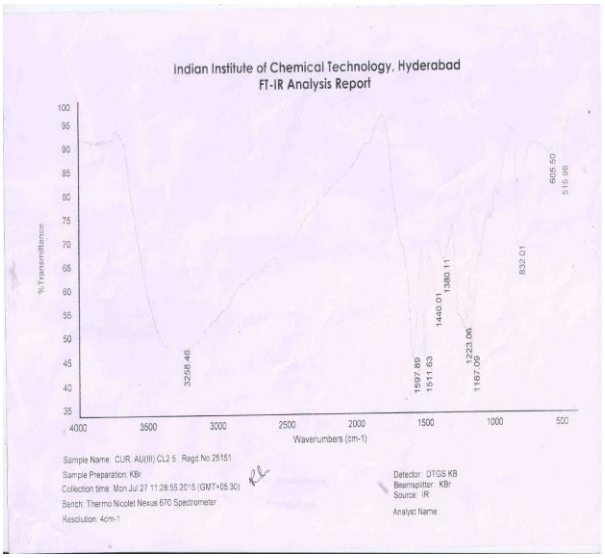


fig.2a

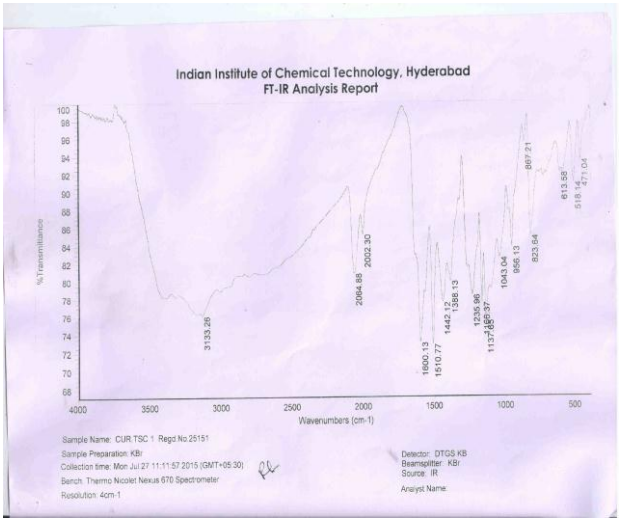


Fig.2b

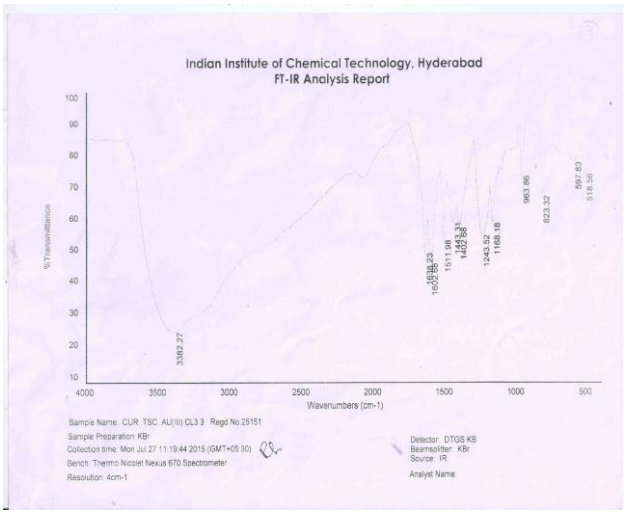


Fig.2c

FT-IR spectra showin (a) curcumin thiosemicarbazone (b) curcumin gold(III)complex

(c) curcumin thiosemicarbazone gold(III)chloride complex

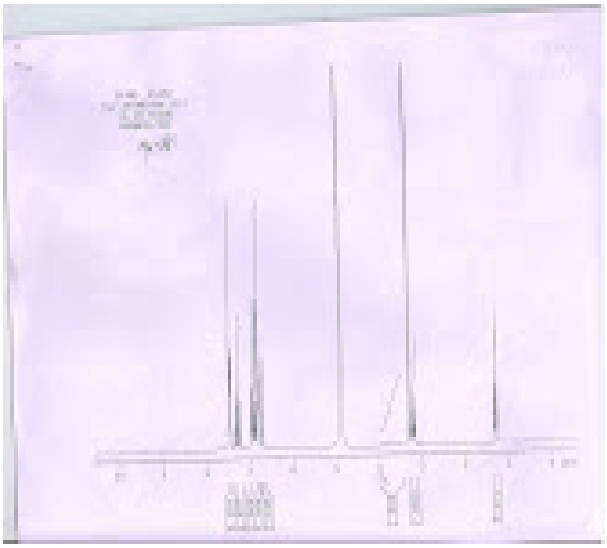


Fig.3a

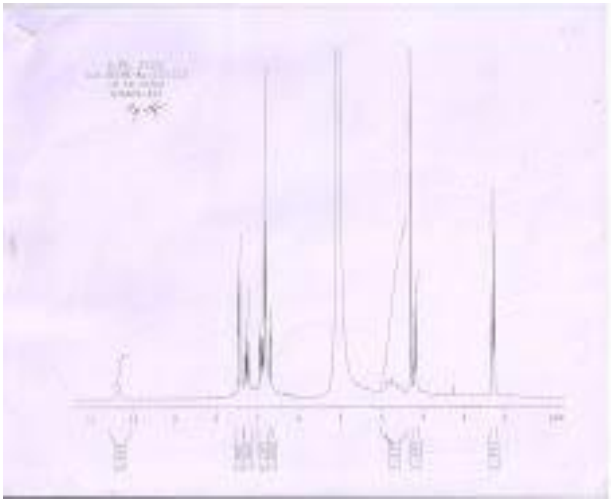


Fig.3b

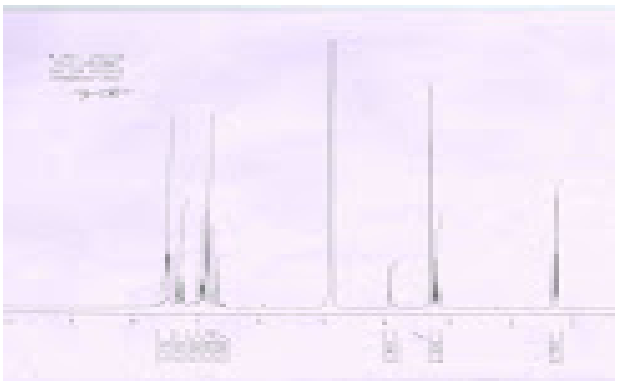


Fig.3c

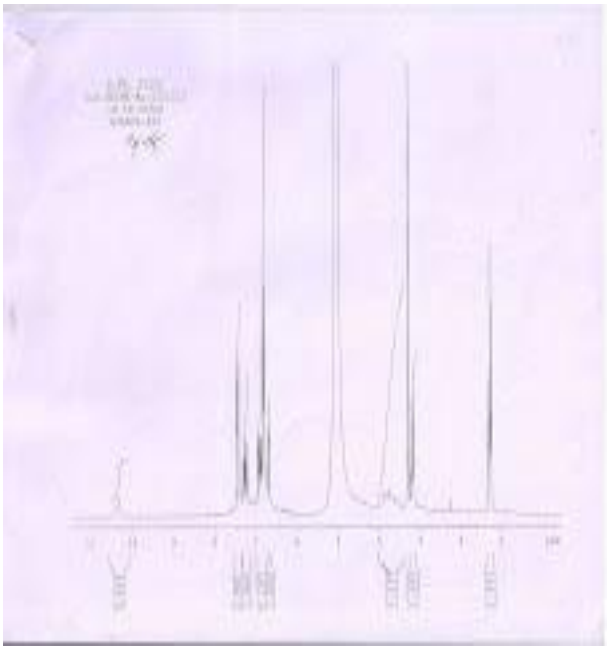


Fig.3ci

HNMR spectra of (a) curcumin thiosemicarbazone
(b) curcumin gold(III)chloride
(c) curcumin thiosemicarbazone gold(III)chloride complex

Mass spectrum

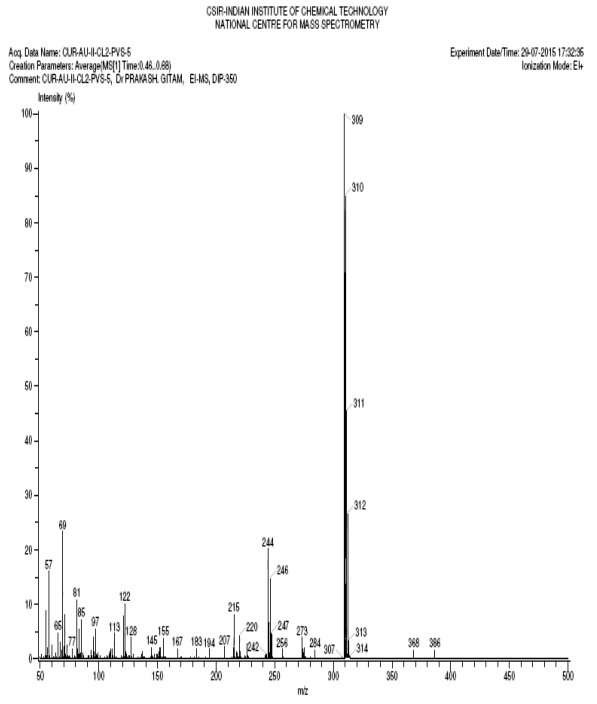


Fig.4 Mass spectrum of curcumin Gold(III)complex

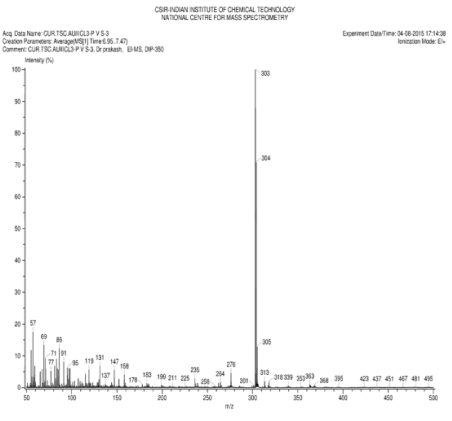


Fig.5 mass spectrum of curcumin thiosemicarbazone Gold(III)complex.

ESR Spectral Analysis

Electronic Spin Resonance(ESR) spectra of Gold(III)complex was recorded in DMF at liquid nitrogen temperature value equal to 30.

Electronic spectra

The structure of the CurTSC Gold(III)complex is Octahedral. By the recent study of X-ray and polarized single crystal spectral studies of the Au(III) ions, these complexes are diamagnetic. They did not show any bands in the electronic spectra.

Biological Activity Studies

The nuclease activity of present ligands and their - complexes has been investigated on pBR 322 plasmid DNA by agarose gel electrophoresis in the presence of H_2O_2. At micro molar concentration, the ligands exhibit no significant activity. The nuclease activity is greatly enhanced by incorporation of metal ions in the ligands. In absence of oxidants, the Gold(III)Complexes of all CURTSC cause discernible DNA cleavage as evidenced by increase in intensity in form 11 (nicked) and form III (linear) with decrease in intensity in form 1 (super coiled) which is attributed to step-wise conversion of form I to form II and to form III Similar observations were also evident in the Gold(III)-Complexes of all CURTSC. The Nuclease Activity of the Gold(III)complexes is more. All complexes show much enhanced nuclease activity in the presence of oxidant, which may be due to free radical reaction (OH*) with DNA. The production of hydroxyl radicals due to the reaction between H_20_2 and the metal complexes. The OH* radical involves oxidation of deoxyribose moiety followed by hydrolytic cleavage of sugar phosphate backbone.

CONCLUSION

We have synthesized Ligands of CURTSC and their complexes with Au(III). All complexes plausible structures are supported by IR, HNMR, ESR and Electronic 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 Au(III) complexes of Curcumin thiosemicarbazone.

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