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## Research Paper

# STRUCTURE AND BIOLOGICAL ACTIVITIES OF NOVEL PHYTOCHEMICALS CU(II)-QUERCETIN THIOSEMICARBAZONE AND ITS DERIVATIVES: POTENTIAL ANTI-CANCER DRUGS

Subrahmanyam Naidu P V<sup>1\*</sup> and Prakash MMS Kinthada<sup>1</sup>

\*Corresponding Author: **Subrahmanyam Naidu P V**, ✉ [pvsnaiduchem@yahoo.com](mailto:pvsnaiduchem@yahoo.com)

Some promising novel phytochemicals quercetin thiosemicarbozone Copper(II)metal complex, quercetin 3-O-glucoside thiosemicarbozone Copper(II)metal complex and their rutin have been synthesized and characterized by elemental analysis by spectral FT-IR, HNMR, ESR, C13NMR, UV-Vis and Mass. The spectral and other data indicate that all the Cu(II) metal complexes are tetrahedral and octahedral(rutin) structure. The quercetin and quercetin 3-O-glucoside thiosemicarbozone ligands(QTSC) and (QOTSC), its Schiff's bases and Copper(II)-metal chelates would be screened *in vitro* for anticancer activity against some cancer cell lines. The transitional metal complexes of Quercetin thiosemicarbozone (QTSC) and Quercetin 3-O-glucoside thiosemicarbozone(QOTSC) ligands possess anti-oxidant, anti-tumor, anti-cancer, anti-viral, anti-malarial, anti-fungal, and anti-microbial. These activities are normally increased upon coordination, so they are suitable ligands for the synthesis of potential anti-cancer agents. In Our present research work, Quercetin derivatives most frequently occurring in the nature to determine the impact of their Chemical structure and Biological Activity. We would further synthesize the schiffs bases of certain of the constituents viz. flavanoids / phytochemicals and later synthesize their Transition metal Complexes especially with Platinum, Gold, Palladium, Ruthenium, Cobalt, Iron, Nickel, Zinc and Chromium. The precursors, the derivatives/Analogues and the Transition metal Complexes, are all excellent candidates as Anticancer Drugs.

**Keywords:** Quercetin Thiosemicarbozone,(QTSC), Quercetin 3-O-glycoside Thiosemicarbozone (QOTSC), Rutin, Cu (II)-metal complexes, Schiff's bases

## INTRODUCTION

Medicinal plants are important substances for the study of their traditional uses through the verification of pharmacological effects and can

be natural composite sources that act as new anti-infectious, anti-oxident agents (Chien-Chang *et al.*, 1993). In order to find out new sources of drugs, a number of medicinal plants have been

<sup>1</sup> Department of Chemistry, Gitam Institute of Technology, Gitam University, Visakhapatnam 530045 AP, India.

screened for wide range of biological activities. About 3,000 materials from 2,764 plant species have been screened for their pharmacological and chemotherapeutic properties (Anon, 1988). Traditionally used medicinal plants produce a variety of compounds of known therapeutic properties (Iyengar, 1976; Harborne, 1989; Chopra *et al.*, 1992). Plants used in ethno medicine for the production of bioactive compounds are used and rationalize the use of these medicinal plants in health care (Morales *et al.*, 2008). Most of their properties are due to secondary metabolites produced by medicinal plants.

World Health Organization (WHO) appreciated the importance of public health care in developing nations. The phytochemicals having important role in the Medicinal plants for Traditional Ayurvedic and Unani systems of holistic health and herbal medicine of the east. Phytochemicals are a fascinating yet mysterious group of thousands of chemicals found in plant foods (Chien-Chang *et al.*, 1993). Some protect against cancer when isolated, some are not associate with cancer at all, and many have yet to be discovered.

The Traditional medicinal plant *Bobgunnia madagascariensis* air-dried powdered of stem barks (400 g) were extracted exhaustively with n-hexane by maceration method. The n-hexane extract concentrated in vacuo yielded a light brown to greenish brown colored oily substance 3.89 g. TLC was carried out on the chloroform extract of *Bobgunnia Madagascariensis* stem bark and was further fractionated using column chromatography. The light yellow colour crystalline derivatives of quercetin and quercetin 3-O-glucoside thiosemicarbozone (QTSC and

QOTSC) has been found to block cell cycle progression in a variety of malignant cell lines including those derived from the prostate, brain, breast, pancreas and colon (Crespy V *et al.*, 2002; and Day *et al.*, 1998). Quercetin derivatives of thiosemicarbozone vincristine and vinblastine is mainly useful for treating Hodgkin's disease, lymphocytic lymphoma, advanced testicular cancer and advanced breast cancer. The thiosemicarbazide and thiosemicarbazone compounds have gained special attention due to their activities against protozoa, influenza and certain kinds of tumors. A large number of thiosemicarbazones have been evaluated for their anti-malarial and anti-tumor activities, because of their useful chemotherapeutic properties (Le Bon and Siess, 2000). In cancer treatment it has been shown that the metal chelates are more potent than the chelating agents (Maeda and Kanazawa, 2002). Metal complexes of Copper containing nitrogen and oxygen donor ligands is found to be effective catalysts for oxidation, reduction, hydrolysis and other organic transformation (Chung *et al.*, 2001). The coordination environment around Copper plays the key role in stabilizing its different oxidation states and hence dictates the redox properties of the quercetin derivatives has been found to block cell cycle progression in a variety of malignant cell lines including those derived from the prostate, brain, breast, pancreas and colon. Quercetin derivatives vincristine and vinblastine is mainly useful for treating Hodgkin's disease, lymphocytic lymphoma, advanced testicular cancer and advanced breast cancer. The thiosemicarbazide and thiosemicarbazone compounds have gained special attention due to their activities against protozoa (Chien-Chang *et al.*, 1993), influenza (Kaur and Kapoor, 2001) and certain kinds of

tumors. Quercetin, quercetin-3-O-glucoside and rutin contribute to the relaxation of smooth muscles in mammals (Erlund *et al.*, 2000). Chemical constituents are used as anti-cancer, anti-tumor, anti-leprotic, anti-oxidant, anti-myotoxic, anti-haemorrhagic, anti-hepatotoxic, anti-viral, anti-bacterial. All complexes are crystalline powders decomposed by mineral acids.

## MATERIAL AND METHODS

The plant *Bobgunnia madagascariensis* sample was authenticated by Dr. Shanmukanada, professor of Bio-technology, GIS, GITAM University, Visakhapatnam and voucher specimen was deposited with Herbarium number 279. These plant materials were cut into smaller pieces, separated into leaves, stem, root barks, and air dried for 3 days in an open place.

The air-dried powdered stem barks (400 g) were extracted exhaustively with n-hexane by maceration method. The n-hexane extract concentrated in *vacuo* yielded a light brown to greenish brown colored oily substance 3.89g. The marc 378 g. was extracted exhaustively by the soxhlet extraction method with chloroform to give a reddish brown extract 43.93 g (11.62%). Preliminary TLC was carried out on the chloroform extract of *Bobgunnia madagascariensis* stem bark and was further fractionated using column chromatography with solvent mixture chloroform: ethyl acetate (1:1), silica Gel particle size 0.13-0.25mm., 60-120 mesh were used for possible isolation of pure components. Chemical characterization of purified active compound, quercetin was done through IR-

8400S spectrophotometer and 200BB NMR spectrophotometer. The obtained spectral data compared to reference standard compound from the library Data base.

## CHEMICALS AND REAGENTS

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 IR spectra were recorded in the range 4000-200  $\text{cm}^{-1}$  using KBr discs with Perkin-Elmer model 1430 and 337. The electrical conductivity measurements were made in DMF (10-3M) at room temperature ( $27 \pm 2^\circ\text{C}$ ) using a Digisun digital conductivity meter (DI-909 model).

The NMR spectra was recorded in DMSO-d<sub>6</sub> on NMR spectrophotometer model JEOL Ex-90 FT 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 ISSfil vibrating sample magnetometer operating at field strength of 2-1.0 kg. High purity nickel metal (saturation moment 55 emu/g) was used as a standard.

## SYNTHESIS OF LIGANDS

A 1x10<sup>-3</sup>M solution prepared by dissolving appropriate amounts of Thiosemicarbazide in 50 mL methanol and 2 mL of glycolic acetic acid was added drop wise to a 5X10<sup>-2</sup>M solution of Quercetin in 50 mL. Methanol while stirring and refluxed for 2-3 h and the product that separated was recrystallized in methanol. Identification of the product was based on elemental analysis, viz., FT-IR, HNMR, C13 NMR, ESR, UV.

## SYNTHESIS OF METAL COMPLEXES

To 30 mL of Cu(II) solution (5x10<sup>-2</sup>M) in methanol was added (1x10<sup>-2</sup>M) QTSC and QOTSC solution in methanol and the mixture refluxed for about 1 hour in a separate reflux arrangement. The solid that separated was filtered and washed with water and re-crystallized with methanol.

## RESULTS AND DISCUSSION

### Characterization of Isolated Compounds

#### (a) IR Spectra

The compound isolated was characterized using IR and NMR spectrophotometric techniques (Le Bon and Siess, 2000). From the analyses, the compound was identified as 3',4',5, 7-tetra hydroxyl flavonol (Quercetin). IR  $\nu_{max}$  (Neat)  $\text{cm}^{-1}$  3282.40 (w), 1743.70 (w), 1666.75 (w), 1610.96 (w), 1517.55 (w), 1430.18 (s), 1358.18 (s), 1210.93 (w), 1094.07 (w), 1001.94(w), 929.56 (w), 882.18 (w), 808.85 (w), 705.01 (w), 590.36 (w).

Quercetin (70eV)  $m/z$  348 [M<sup>+</sup>], 302(98), 257(15), 228(8), 201(8), 154(8), 136(9), 110(9), 70 (4) and 23 (3). M-N, M-Cl bonds are 213, 226  $\text{Cm}^{-1}$ ; C=S: 456  $\text{Cm}^{-1}$ ; C=N: 1610  $\text{Cm}^{-1}$ . These suggests a metal complex nucleus.

**Compound was obtained as a crystalline yellow solid (m.pt. 315oC).**

The 1H-NMR  $\delta$ (CD3OD): 6.18(1H, d, J=1.7Hz), 6.40(1H, d, J=1.7Hz) are due to meta-coupled protons of A-ring (H-6 and H-8) of a flavonoid nucleus.

Signals at  $\delta = 6.89$  d =8.3Hz, 7.68d, 2.5Hz and  $\delta = 7.55$ dd, 2.2Hz, 8.3Hz were assigned to H-5', H-2' and H-6' of the ring. The 1H NMR spectrum showed protons at aromatic regions from 6-8ppm, and strong hydrogen bonding at 12.5ppm.

These suggests a quercetin nucleus.

The NMR spectrum of metal chelates confirms the non participation of NH<sub>2</sub> group in the coordination with metal ions. 1H NMR signals are well defined and the spectrum of ligand [28] exhibits two resonances for the NH<sub>2</sub> protons at 7.8 ppm, a result explained in terms of hindered rotation about the C(S)-4NH<sub>2</sub> bond due to its partial double bond character (Clarke, 2003; and Clarke, 1980). The metal complexes show only one resonance due to 4,NH<sub>2</sub> protons, upfield for some complexes (at 9.46, 8.30, 8.23) and down field (at 9.72) for some complexes.

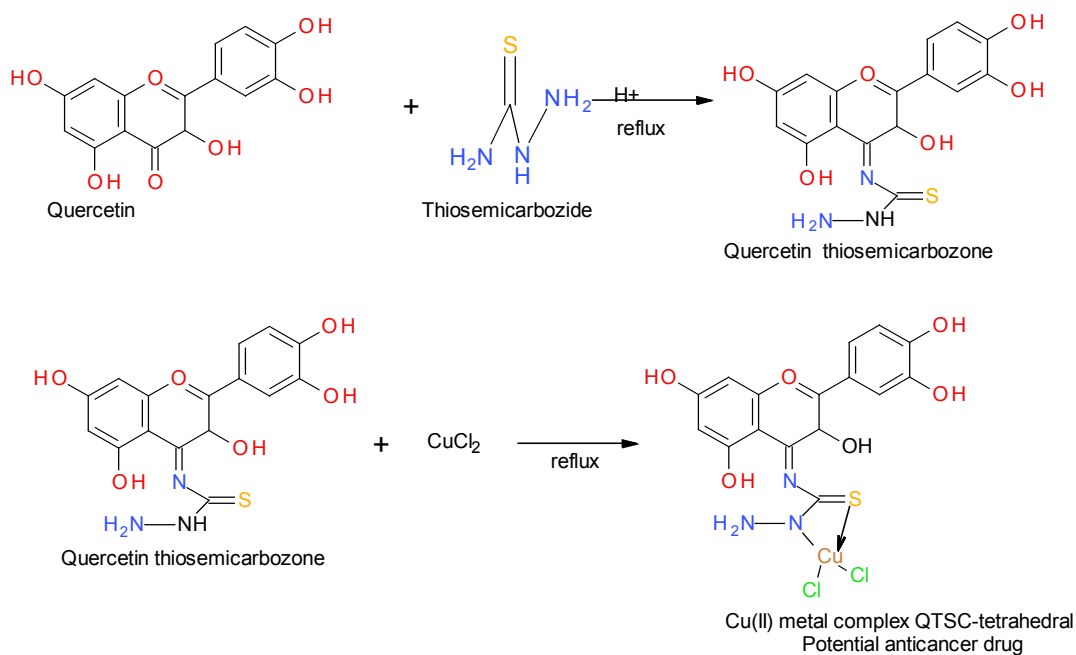
The signal at 11.90ppm in the spectrum of ligand due to 2NH is present in most of the complexes with down field shifts (11.40, 11.43, 11.63) and with an up field shift for one complex (12.41) probably indicating a change in the nature of NH resonance complexes.

#### (b) 13C-NMR spectra analysis

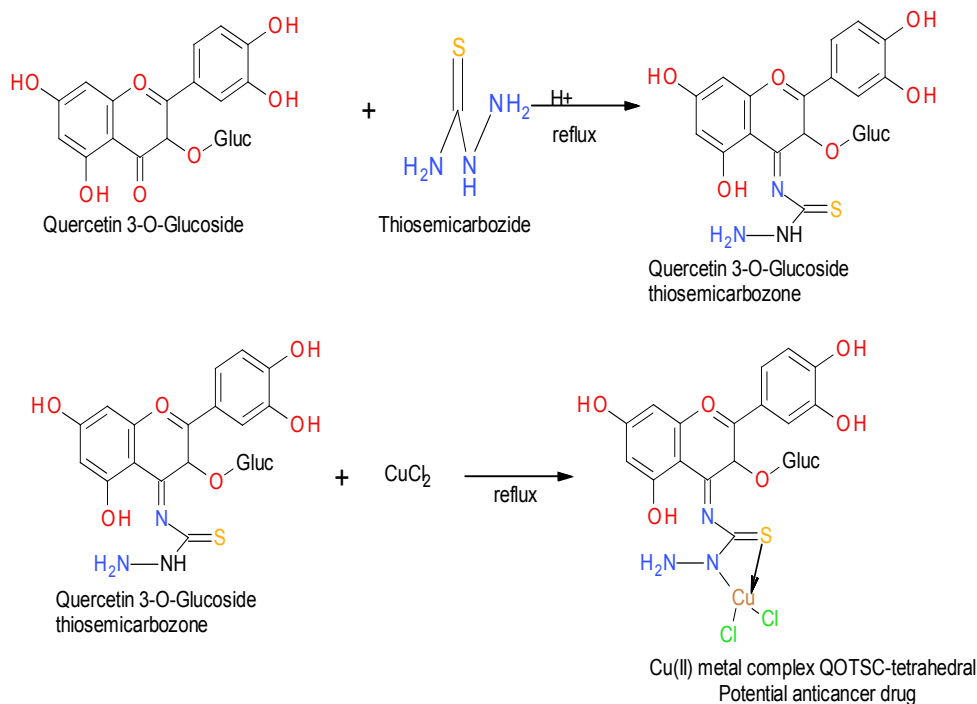
15, carbon signals typical of flavonoid monoglycoside nucleus.

Two protons of the NH<sub>2</sub> group 11.179 ppm (S, IH, -NH). 11.824 ppm (S, IH, -NH). These suggests a Thiosemicarbozone nucleus.

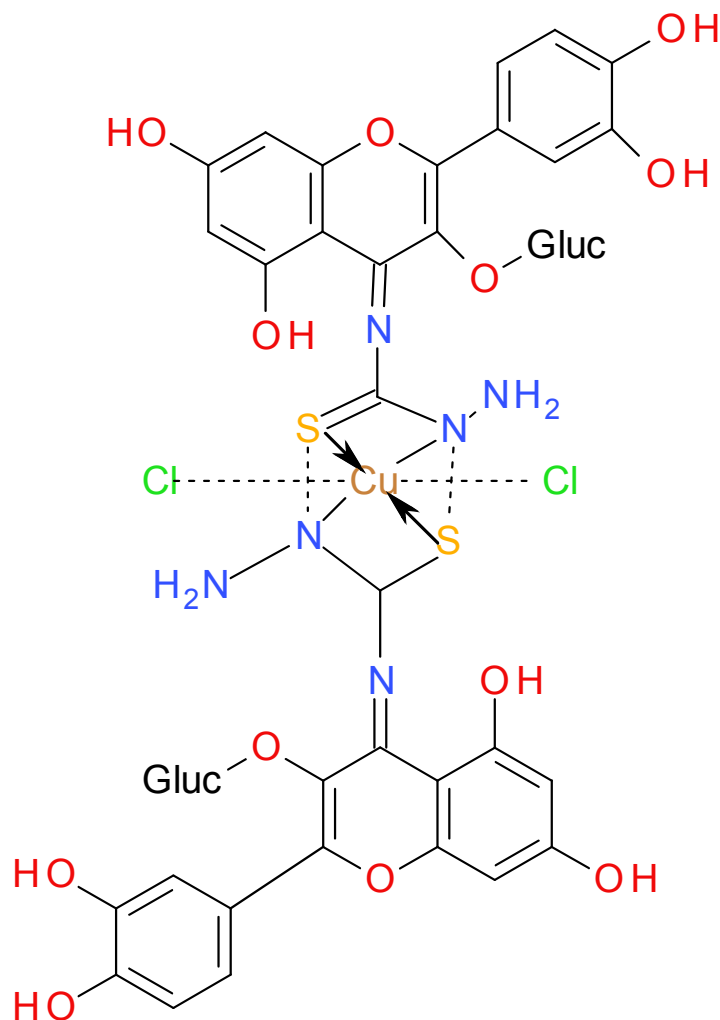
### Synthesis of Cu(II)-Metal Complex of QTSC(Novel)



### Synthesis of Cu(II)-Metal Complex of QOTSC(Novel)



### Synthesis of Cu(II)-Metal Complex of Rutin(Novel)



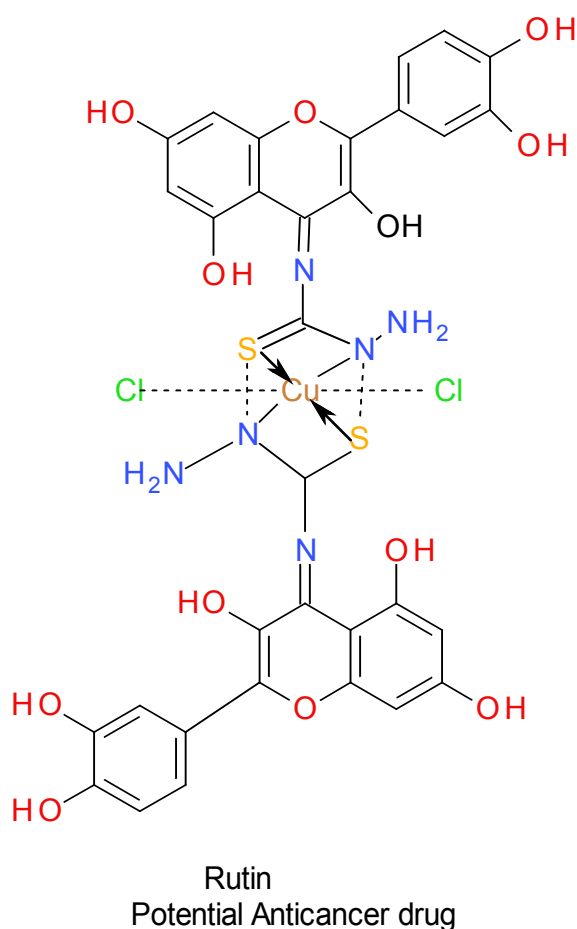
### Rutin Potential Anticancer Drug

$^{13}\text{C}$ -NMR spectral data was indicated in all the complexes downfield or up field chemical shifts were obtained for the carbon resonances adjacent to the assumed coordination sites while the others remain essentially unchanged. The affected carbon resonances in the ligands were shifted or absent, supports coordination.

All the metal complexes were stable at room temperature non hygroscopic, sparingly soluble

in methanol or ethanol and fairly soluble in DMF and DMSO. The analytical data for ligand and metal chelates were consistent with their proposed molecular formulae

The signal at 11.90ppm in the spectrum of ligand due to 2NH was present in most of the complexes with down field shifts (11.40, 11.43, 11.63) and with an up field shift for one complex (12.41) probably indicating a change in the nature

**Synthesis of Cu(II)-metalcomplex of rutin(novel):**

of NH resonance complexes. The signal at 11.90ppm in the spectrum of ligand due to 2NH was present in most of the complexes with down field shifts (11.40, 11.43, 11.63) and with an up field shift for one complex (12.41) probably indicating a change in the nature of NH resonance

**(c) Electron spin resonance(ESR) - spectral analysis**

Electronic Spin Resonance(ESR) spectra of Copper(II)complex was recorded in DMF at liquid nitrogen temperature value equal to 18.

**Electronic spectra:** In square planar complexes of Cu(II), two energy level sequences 34,35]viz.  $d_{z^2} < d_{x^2} < d_{y^2} < d_{xy} < d_{x^2-y^2}$  and  $d_{x^2} < d_{y^2} < d_{z^2} <$

$d_{xy}, d_{x^2-y^2}$  have been suggested. The former has recently been studied by X-Ray and polarized single crystal spectral studies (Gim, 1967) of the Palladium Ions. Three spin allowed d-d transitions from the three lower lying d levels to the empty  $d_{x^2-y^2}$  orbitals are predicted on the basis of this sequence. Accordingly the bands observed in the regions 16,100-23,800; 23,800-28,900; 28,900-35,400 $\text{cm}^{-1}$  may be assigned to the transitions  $1A_{1g}-1A_{2g}, 1B_{1g}-1B_{1g}, 1A_{1g}-1E_{1g}$ , respectively. The peaks observed for the Copper(II) complexes at 22, 240-222, 260, 27800-28200 and 37,046-37,200 $\text{cm}^{-1}$  support the Tetrahedral geometry.



**(d) Magnetic studies**

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

**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/absence of H<sub>2</sub>O<sub>2</sub>. At micro molar concentration, the ligands exhibit no significant activity in absence and in the presence of the oxidant as shown in Figure 1. The nuclease activity was greatly enhanced by incorporation of metal ions *m* the ligands. In absence of oxidants, the Cu(II)-complexes of QTSC and QOTSC substituted Thiosemicarbazones cause discernible DNA cleavage as evidenced by increase in intensity in form 11 (nicked) and form III (linear) with decrease in intensity in form I (super coiled) which is attributed to step-wise conversion of from I to form II and to form III. Similar observations were also evident in the Copper(II)- Complexes of QTSC & QOTSC and Substituted TSCs. The nuclease activity of the Cu(II) complexes with QTSC & QOTSC is more. All complexes shows much enhanced nuclease activity in the presence of oxidant, which may be due to free radical reaction (OH<sup>\*</sup>) with DNA. The production of hydroxyl radicals due to the reaction between H<sub>2</sub>O<sub>2</sub> and the metal complexes. The OH<sup>\*</sup> radical involves oxidation of de-oxy ribose moiety followed by hydrolytic cleavage of sugar phosphate backbone (Sava *et al.*, 2002). On the basis of physicochemical and spectral data the metal chelates are assigned to be Octahedral complexes.

The Formulae of the complexes could be written as : [ML] n

where M = Cu(II) :

L=QTSC, QOTSC and substituted TSCs

**CONCLUSION**

we have synthesized Ligands; L=QTSC, QOTSC, and their complexes with Cu(II). All complexes's plausible structures were supported by LSI Mass spectral data along with physico-chemical and IR, NMR, Mass, ESR, 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 Cu(II) complexes of Quercetin Thiosemicarbazone, Quercetin 3-O-glucoside and Substituted Quercetin Thiosemicarbazones.

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