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Copper Conjugates of Knoevenagel Condensates of Curcumin and their Schiff Base Derivatives: Synthesis, Spectroscopy, Magnetism, ESR, and Electrochemistry

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Novel copper(II) complexes of curcumin Knoevenagel condensates and their Schiff bases have been synthesized and characterized. All copper complexes possess distorted square-planar geometries with 1:1 metal to ligand stoichiometry capable of stabilizing Cu^{2+}/Cu^{1+} redox couples in the range 0.34 to 0.40 V. ESR spectral features are consistent with $g_{\|} > g_{\perp} > 2.0$ suggesting monomeric nature of copper complexes having $d_{x^2-y^2}$ ground state.

Keywords curcumin, thiosemicarbazones, copper(II) complexes, redox properties, Knoevenagel condensation

INTRODUCTION

Curcumin, (1,7-bis(4-hydroxy-3-methoxy phenyl)-1,6-heptadiene-3,5-dione, **1**) is an active principle of turmeric (*Curcuma Longa Linn.*) which has a long history of medicinal use in the middle East and India. Extensive scientific research on **1** have demonstrated anti-inflammatory[1] anticancer,[2] and potent antioxidant[3] activities apart from its promising role in variety of disease conditions including AIDS, Alzheimer's disorders.[4] The polyphenolic compound is pharmacologically safe even when administered at doses up to 10 g/day[5] and hence has enormous potential in the prevention and therapy of variety of acute diseases and chronic disorders.

However, it exhibits low oral bioavailability and undergoes rapid first-pass metabolism and excretion in the bile.[6] In order to circumvent the problems associated with low bioavailability extensive efforts have been made to evolve various drug delivery strategies including structural modifications of **1**. In our laboratory, we have encapsulated curcumin with hydrophilic jellose polymer, which leads considerable enhancement in the bioactivity rather than the parent compound. This has encouraged us to undertake derivatization of diketo motif of curcumin by employing hydrophilic metalloid scaffold. The enolizable ketonic function of **1** has long been known to form complexes with various metal ions and metalloids.[7–10]

In order to impose some selectivity in these interactions it is necessary to introduce different donor functionalities in metal coordination other than oxygen by modifying the diketonic functions. This task can be facilitated by condensation of its active methylene group with an aldehydic group giving a non-enolisable Knoevenagel condensate that can then be effectively reacted with appropriate functionality generating corresponding Schiff bases as shown in Scheme 1.[10]

In the present communication we describe synthesis, molecular characterization and redox behavior of copper(II) complexes of curcumin-thiosemicarbazone Schiff bases. Due perhaps to sulphur-nitrogen donor functionalities in these ligands they have preferential affinities for softer copper metal ions yielding very stable metal conjugates. In most cases the compounds possess distorted square planar geometries with facile Cu^{2+}/Cu^{+} redox couples functionally useful and adaptable under biological systems. The redox behavior is found to be dependent on coordination geometry and donor atoms set around the central metal ion[11,12] and good

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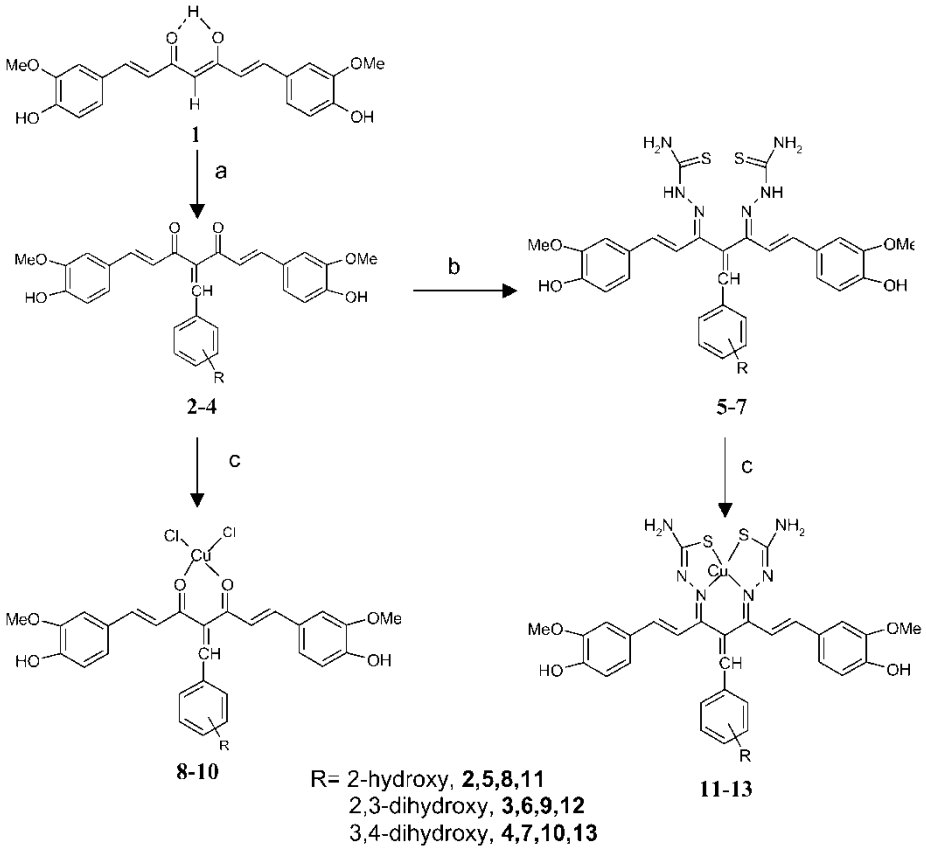

SCH. 1. Synthetic steps used in the preparation of copper conjugates of Knoevenagel condensates and Schiff bases of **1**. Specific conditions followed for various steps include: (a) piperidine, 48 hrs, methanol; (b) $H_2NCSNHNH_2 \cdot HCl$, 24 hrs, piperidine, methanol, room temp. (1:2); (c) $CuCl_2 \cdot 2H_2O$, methanol, piperidine (1:1).

structure-activity relationship is observed between ESR parameters and the distortion factor calculated.

RESULTS AND DISCUSSION

Synthesis

Curcumin (**1**) is available commercially as a mixture of three curcuminoids and hence was separated from its demethoxy and *bis*-demethoxy analogs by column chromatography over silica gel using chloroform:methanol (9:1) as eluting solvent. The intramolecular hydrogen bonding in **1** restricts the diketone moiety to take part in derivatization with condensable amines. It can, however, be carried out by condensing its active methylene group with aldehydes to yield non-enolisable β-diketone by a reaction known as Knoevenagel condensation.[10,13]

In the present work methylenic proton of the β-diketone moiety was replaced by various hydroxy aromatic aldehydes with good yields. The condensates were reacted with thiosemicarbazide side chains in the molar ratio of 1:2 to yield bis-Schiff base ligands. Interactions of these Schiff base ligands with copper chloride resulted in mono-ligand copper complexes having a general molecular formula $C_{30}H_{30}CuN_6O_{5\text{-}6}S_2$. They exhibit negligible solution conductivity (9-42 $m\Omega^{-1}$ cm^2 $mole^{-1}$) in DMSO solvent indicating their non-electrolyte nature.[14]

NMR Studies

In the NMR spectrum of **1** the strong signal at δ 5.7 ppm due to methylenic protons is lost upon Knoevenagel condensation (**2**–**4**). As anticipated ^{1}H-NMR spectra of Schiff bases **5**–**7** do not show any resonance attributable to the S-H proton at δ 4.0 ppm,[15] but instead show a singlet at δ 13.70 ppm due to the intramolecular hydrogen-bonded thiohydrazinic (N-H) proton indicating existence of the thione form in DMSO solvent.[16,17] This absorption is absent in the spectra of the complexes consistent with deprotonation of the thiosemicarbazide chain confirming coordination through the thiolate form.

A broad singlet appearing at $\sim\delta$ 3.0 ppm is ascribed to the terminal NH_2 group suggesting their involvement in hydrogen bonding interactions. The partial double bond character for the C-NH_2 linkage restricts free rotation and makes the two protons magnetically inequivalent resulting in broadening of the signal.[18] In the spectra of the corresponding metal complexes the singlets are shifted downfield implying lowering of the bond order as a consequence of thione $\Rightarrow$ thiol tautomerization during complexation.[19]

Infrared Spectra

IR spectrum of **1** in its stable enolisable form exhibits the carbonyl stretching frequency at 1620 cm^{-1} and an intramolecularly hydrogen bonded hydroxyl absorption at 3379 cm^{-1}. In the Knoevenagel condensates (**2**–**4**) the carbonyl stretch appears at 1655–1633 cm^{-1} while the hydroxyl absorption is found to be absent. Introduction of thiosemicarbazone side chains into the Knoevenagel condensates (**5**–**7**) is best diagnosed from the disappearance of carbonyl frequency and occurrence of additional bands at 1595 and 870 cm^{-1} ascribed to azomethine and thiocarbonyl stretching frequencies, respectively.

The bisthiosemicarbazone derivatives are known to exhibit thione ⇋ thiol tautmerism due to the presence of a thioamide group. The absence of the ν(S-H) band near 2750 cm^{-1} and presence of ν(N-H) stretching frequency between 3751–3349 cm^{-1} indicate that ligands **5**–**7** exist as thione tautomers in the solid state.[20] The thiolic absorption is found to be absent in the IR spectra of metal complexes indicating deprotonation of the thiosemicarbazide side chain and subsequent coordination through thiolate anion.[21]

The absorptions at 3250 and 3150 cm^{-1} are attributed to the asymmetric and symmetric stretching frequencies of the terminal NH_2 group which exhibit appreciable changes upon metal coordination due to involvement of the thioamide sulfur in complexation.[22] Similarly the imino frequency of the thiosemicarbazide side chains is shifted to lower frequency upon metal coordination indicating involvement of imine nitrogen in metal coordination.[23] The bands in the region 448–435 and 352–345 cm^{-1} are ascribed to Cu-N and Cu-S stretches respectively.

Electronic Spectra and Magnetic Studies

Present curcumin derivatives exhibit strong absorptions around ~30800 cm^{-1} and 24000 cm^{-1} attributed to the intraligand π-π^* and n-π^* transitions respectively.[24] For the copper conjugates **11**–**13**, the former were shifted to lower energy side indicating enolisation of the thiocarbonyl group which is commonly observed in the thiolato binding of thiosemicarbazone complexes.

For square-planar copper complexes with a $d_{x^2-y^2}$ ground state, three spin-allowed transitions are expected, viz., $^2B_{1g} \rightarrow {}^2A_{2g}$ ($d_{x^2-y^2} \rightarrow d_{z^2}$), $^2B_{1g} \rightarrow {}^2B_{2g}$ ($d_{x^2-y^2} \rightarrow d_{xy}$) and $^2B_{1g} \rightarrow {}^2E_g$ ($d_{x^2-y^2} \rightarrow d_{xy,yz}$) respectively, which, however, are difficult to resolve due to their comparable energies and difficulties in distinguishing individual transfers.[25,26] In case of present copper complexes of the Knoevenagel condensates **8**–**10**, the absorption in the region 17,000–20,000 cm^{-1} is assigned to $d_{x^2-y^2} \rightarrow d_{z^2}$ transition which is shifted towards lower energy in the bis-thiosemicarbazonate metal conjugates. The absorption between 21,000–25,000 cm^{-1} corresponds to the intense LMCT charge transfer band, which is characteristic feature commonly associated with metal-thiosemicarbazone complexes.[27,28] Room temperature magnetic moments (μ_{eff}) of all copper(II) complexes described presently fall in the range of 1.76–1.82 B.M. corresponding to the spin only value for monomeric square planar complexes.[36]

Electrochemistry

The electrochemical profile of **1** shows a quasi-reversible peak centered at −0.84 V ascribed to the reduction of its carbonyl functions.[7] On Knoevenagel condensation, this peak is shifted to positive side and an additional peak is observed at −1.6 V due to reduction of azomethine functionality.[29] Analysis of the cyclic voltammetric profiles of all copper conjugates indicates ip_a/ip_c ratio approximately equal to unity for the well-defined Cu^{2+}/Cu^{+} redox couple centered between +0.33 to +0.40 V.

The scan rate dependence of this peak is shown in the inset of Figure 1, which confirms its reversible nature. In the absence of either uncompensated solution resistance or anomalous electrode surface effects, the departure of ΔE_p from 0.059 V observed in some of the present copper complexes is indicative of significant

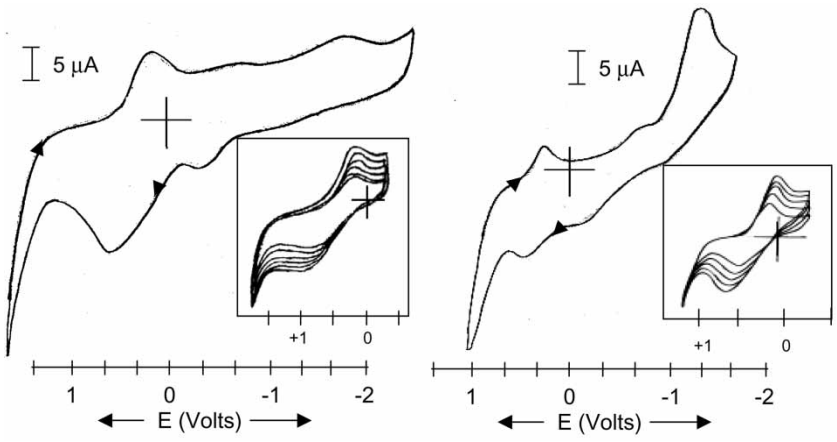

FIG. 1. Cyclic voltammogram of **8** and **11** (v = 100 mV/s) in DMSO where *Inset* shows scan rate dependence of the copper redox couple.

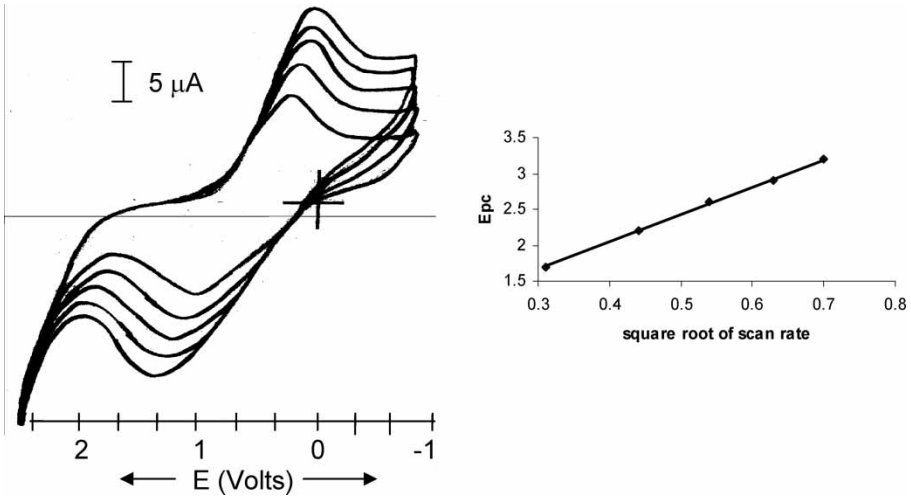

FIG. 2. Cyclic voltammogram of **11** in DMSO with TEAP as supporting electrolyte at 100–500 mV s^{-1}. *Inset* plot of square root of scan rate *versus* cathodic current.

geometrical reorganization accompanying the redox changes.[30] It is known that the Cu(II)/Cu(I) couple experiences some structural reorganization barrier in view of the rearrangement from square-planar Cu(II) to pseudo-tetrahedral Cu(I) geometries. The effects of stereochemical changes on redox potentials are directly correlated to conversion of square-planar copper(II) species to tetrahedral Cu(I) products.

The redox potentials observed for the present series of complexes indicate a moderate strength for bis-thiosemicarbazonates to sustain these changes. It implies that greater deformation in the chelate rings of a coordinated thiosemicarbazone ligand induces substantial departure from square-planar geometry with more difficulty in stabilizing the Cu(I) state. The potentials of Cu(II)/Cu(I) couple of the present series of complexes are notably shifted than expected may be due to the difference in the chemical environment and the chromophore around the Cu(II) ions.

Nevertheless, it is likely attributable not only to inductive electronic factors of the redox active diketone moiety but also because of columbic effects such as formation of charged or neutral sulfur donor sites. However, the anodic (Ep_a) peak potentials of copper complexes (**8**–**10** and **11**–**13**) in the positive region are comparable with copper complex of naturally occurring curcumin and synthetic models containing S-donor ligands.[7] The cathodic peak current was found to be proportional to the square root of the scan rates indicates that the charge transfer process are diffusion controlled, which is confirmed by the observed linear plot of (Figure 2) square root of the scan rate versus cathodic peak current.

The ligand system with extended π orbitals and the distortions in the copper geometry might have forced the central copper to reduce at a positive reduction potential. The redox process associated with oxidation of Cu(I) to Cu(II) for **11**–**13** seems to be more significant ($E_{1/2} = 0.4–0.3625$ V) than **8**–**10** may probably originate due to the presence of a thione/thiol sulfur center and redox active diketone moiety. Since both the diketone moiety and the thiosemicarbazide side chain are flexible, the ligand can adopt different conformations so as to fit the smaller sized Cu(II) ions, thus favoring the oxidation process appreciably.

Moreover, this oxidation step results in the formation of Cu(II) with a preference for a square-planar geometry. The extent of electrochemical stability may be assessed from the correlation (Figure 3) between the $E_{1/2}$ values with that of the degree of tetrahedral distortion (F) for the Cu(II)/Cu(I) redox couples. A linear relationship observed for these copper compounds indicates that departure from a square-planar stereochemistry leads to destabilization of the copper(I) species formed in the solution.

ESR Studies

The X-band EPR spectra of all copper conjugates were recorded in DMSO glass at 77K (see Figure 4) and the spin

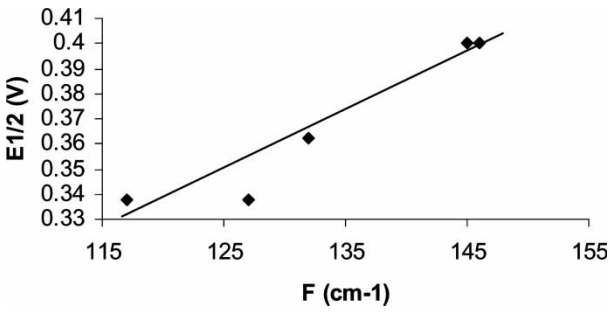

FIG. 3. Correlation of degree of tetrahedral distortion (F in cm^{-1}) against Cu^{2+}/Cu^{1+} redox potentials ($E_{1/2}$ in volts). The straight line represents the best-fit curve.

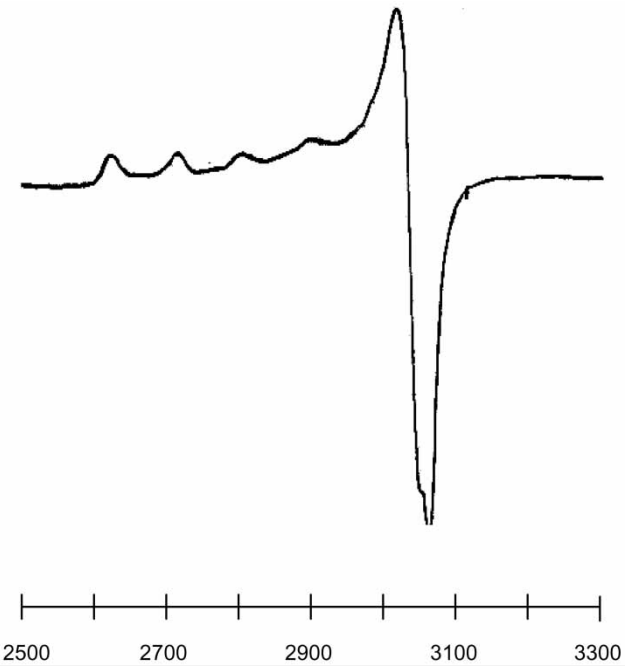

FIG. 4. EPR spectrum of compound **8** in DMSO at 77 K.

Hamiltonian parameters calculated for these are summarized in Table 1. All compounds exhibit a well-resolved four-line copper hyperfine pattern and follow the relationship $g_{\parallel} > g_{\perp} > 2.0$ characteristic of monomeric planar copper complexes. Kivelson and Niemen have pointed out that compounds having $g_{\parallel} \geq 2.3$ are ionic while those with $g_{\parallel} < 2.3$ are covalent in character.[31]

The $g_{\parallel}$ values for the present series of complexes reveal appreciable covalency with $d_{x^2-y^2}$ as the ground state. EPR parameters also reflect the degree of tetrahedral distortion for square-planar copper(II) complexes. It has been observed that increase in $g_{\parallel}$ values with concomitant decrease in $A_{\parallel}$ components leads to an increase in the tetrahedral distortion and the degree of distortion defined by the parameter $F = g_{\parallel}/A_{\parallel}$, which is regarded as an index of deviation from idealized geometry. The values of 110–120 cm^{-1} are typical for square planar complexes, while the range of 130–150 cm^{-1} is characteristic of slight to moderate distortion and 180–250 cm^{-1} indicate considerable distortion.[32,33] The values observed for the present series of compounds (117–156 cm^{-1}) suggest a moderate distortion.

Figure 5 depicts the correlationship between $g_{\parallel}$, $A_{\parallel}$ and F, as a consequence of the destabilization of the square-planar geometry. Moreover, this tetrahedral distortion influences the copper hyperfine structure, suggesting that the unpaired electron is asymmetrically delocalized along the chelate rings. Thione sulfur binding probably induces more structural deformations leading to substantial departure from the planar geometry. While on the other hand, the thiol sulfur enforces the structure to remain in a nearly square-planar geometry[34] Such a difference may originate from the fact that thiolato sulfur binding incorporates greater covalency in the metal-ligand bonding through delocalized $d\pi$-$p\pi$ in-plane π-bonding as well as σ-bonding interactions.

EXPERIMENTAL

Materials

All reagents and solvents were of reagent grade or were purified by standard methods prior to use.[35] Curcumin was a commercial product Sigma (St. Louis, MO), which also contained demethoxycurcumin, and bisdemethoxycurcumin, respectively. Curcumin was separated and isolated from it by column chromatography using silica gel 60 (Merck 60-120 mesh) monitored through thin layer chromatography (TLC) on pre-coated silica gel plates (Merck) using chloroform: methanol (9:1) as developing system.

Physical Measurements

^{1}H-NMR spectra were recorded on a FT-NMR Varian Mercury YH-300 Spectrometer. Unless otherwise specified

TABLE 1
Magnetic, ESR and electrochemical data on copper conjugates of Knoevenagel condensates and Schiff bases

Parameter	**8**	**9**	**10**	**11**	**12**	**13**
$\mu_{eff.}$ (B.M.)	1.76	1.79	1.82	1.80	1.77	1.80
Ep_c (V)	0.200	0.125	0.125	0.250	0.075	0.250
Ep_a (V)	0.475	0.550	0.600	0.475	0.725	0.550
$E_{1/2}$ (Cu^{2+}/Cu^{+})	0.3375	0.3375	0.3625	0.3625	0.4000	0.4000
ΔE_p	0.275	0.425	0.475	0.225	0.655	0.300
$\%i_{pc}/i_{pa}$	90	80	95	77	96	88
$g_{\parallel}$	2.212	2.232	2.260	2.280	2.291	2.294
$g_{\perp}$	2.069	2.073	2.077	2.066	2.070	2.072
$A_{\parallel}$(G)	188	175	170	157	156	147
F(cm^{-1})	117	127	132	145	146	156

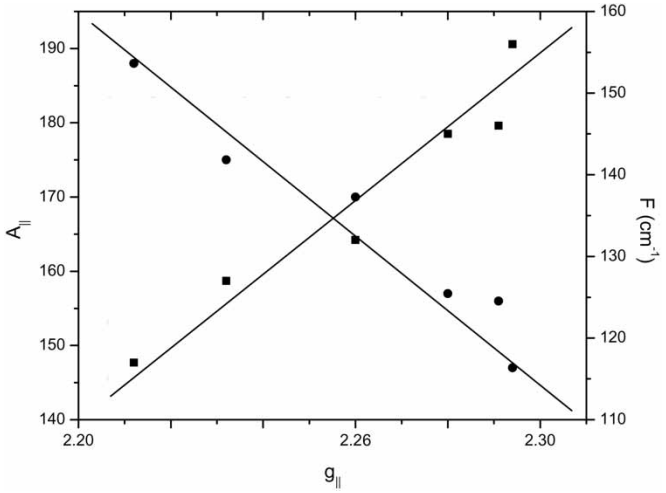

FIG. 5. Variation of $g_{\parallel}$ with $A_{\parallel}$ and degree of tetrahedral distortion (F). The straight lines represents the best-fit curve.

all NMR spectra were obtained in deuterated chloroform ($CDCl_3$) and referenced to the residual solvent peak. In order to examine thione ⇋ thiol tautomerism of thiosemicarbazide ligands and their copper complexes ^{1}H-NMR spectra were also recorded in polar solvent like D_6-DMSO. IR spectra were recorded using KBr pellet on FTIR-8400 Schimadzu spectrophotometer. Electronic spectra were recorded between 200 to 1000 nm (cm^{-1}) in DMSO solvent using identical quartz cuvettes on double beam UV-1601 Spectronic Genesys 2 UV-Vis spectrophotometer.

All electrochemical measurements were made in 10 mM DMSO solvent using 0.1 M tetraethyl ammonium perchlorate (TEAP) as a supporting electrolyte on BAS cyclic voltammetric model CV-27 with automatic system under dry and pure nitrogen atmosphere. The three-electrode system employed consisted of platinum as working electrode, platinum wire as auxiliary electrode and standard calomel electrode (SCE) as a reference electrode. The SCE was calibrated with the ferricinium/ferrocene redox couple located at $E_{1/2} = +0.40$ V ($\Delta E_p = 0.06$ V).

The X-band ESR spectra were recorded on a Varian ESR spectrometer with 100 KHz field modulation frequency and the instrument was calibrated with DPPH standard. Elemental analyses were performed on Hosli Holland CHN analyzer. The magnetic susceptibility was measured at room temperature on a Faraday type magnetic balance with a permanent magnetic field of 7000 G and the instrument was calibrated with $Hg[Co(SCN)_4]$ standard compound.

General Procedure for Preparation of Various Knoevenagel Condensates (2–4)

To the purified curcumin (368 mg, 1 mmol) dissolved in minimum amount of chloroform:methanol (9:1) mixture in a round bottom flask (RBF) was added a methanolic solution of aromatic aldehyde (1 mmol) in a dropwise manner with continuous stirring and catalytic amount of piperidine (0.05 cm^3). The reaction mixture was stirred for 48 hr and set aside for the product separation. The compounds were washed with excess of petroleum ether-hexane and were recrystallized from chloroform-hexane mixture to give pure dark brown Knoevenagel condensates.

4-Salicylidene-1,7-bis (4-hydroxy, 3-methoxyphenyl)-1,6-heptadiene-3,5-dione (2). Yield: 76%, mp: 96–98 °C, ^{1}H-NMR ($CDCl_3$): δ 3.73 (s, 6H, OCH_3), 6.66 (s, 2H, ArH), 6.71 (dd, 4H, $J = 7.8$, 7.8 Hz, ArH), 7.1 (d, 2H, $J = 15.6$ Hz, =C-H), 7.6 (d, 2H, J=15.6 Hz, H-C=), 7.49 (m, 4H, ArH), 7.98 (s, 1H, =CH-Ar); IR (KBr, cm^{-1}): ~3400 ($\nu_{O\text{-}H\ br.}$), ~3012, 2945 ($\nu_{=C\text{-}H,\ C\text{-}H}$), ~1633($\nu_{C=O}$), ~1508 ($\nu_{C=C}$), ~1388, 1029 ($\nu_{C\text{-}H}$), ~975 ($\nu_{H\text{-}C=C\text{-}Htrans}$), ~821 ($\nu_{C\text{-}H\ aro.}$); UV-Vis: λ_{max} (nm, DMSO): 327; MS (+ES-MS): m/z = 472.48 (475) (M + 2); Anal. Calc. (Found): $C_{28}H_{24}O_7$; C, 71.18 (71.07); H, 5.12 (5.20%).

4-(2,3-dihydroxy benzyl)-1,7-bis (4-hydroxy, 3-methoxyphenyl)-1,6-heptadiene-3,5-dione (3). Yield: 63%, mp: 79–81°C, ^{1}H-NMR ($CDCl_3$): δ 3.82 (s, 6H, OCH_3), 6.97 (m, 2H, ArH), 6.80 (m, 6H, $J = 8.62$ Hz, ArH), 6.42 (d, 2H, $J = 15.6$ Hz, =C-H), 7.54 (d, 2H, J=15.4 Hz, H-C=), 7.34 (d, 1H, $J = 8.62$ Hz, ArH), 7.98 (s, 1H, =CH-Ar); IR (KBr, cm^{-1}): ~3417 ($\nu_{O\text{-}H\ br.}$), ~3050, 2947 ($\nu_{=C\text{-}H,\ C\text{-}H}$), ~1655 ($\nu_{C=O}$), ~1514 ($\nu_{C=C}$), ~1382, 1029 ($\nu_{C\text{-}H}$), ~977 ($\nu_{H\text{-}C=C\text{-}Htrans}$), ~819 ($\nu_{C\text{-}H\ aro.}$); UV-Vis: λ_{max} (nm, DMSO): 329, 428; MS (+ES-MS): m/z = 488.48 (490) (M + 1); Anal. Calc. (Found): $C_{28}H_{24}O_8$; C, 68.85 (68.78); H, 4.95 (4.82%).

4-(3,4-dihydroxy benzyl)-1,7-bis (4-hydroxy, 3-methoxyphenyl)-1,6-heptadiene-3,5-dione (4). Yield: 80%, mp: 104–106°C, ^{1}H-NMR ($CDCl_3$): δ 3.83 (s, 6H, OCH_3), 6.80 (m, 6H, ArH), 7.38 (m, 3H, ArH), 7.98 (s, 1H, =CH-Ar), 6.43 (d, 2H, J=14.85 Hz, =C-H), 7.54 (d, 2H, J=15.68 Hz, H-C=); IR (KBr, cm^{-1}): ~3500 ($\nu_{O\text{-}H\ br.}$), ~2929, 2856 ($\nu_{=C\text{-}H,\ C\text{-}H}$), ~1633 ($\nu_{C=O}$), ~1521 ($\nu_{C=C}$), ~1382, 1028 ($\nu_{C\text{-}H}$), ~954 ($\nu_{H\text{-}C=C\text{-}Htrans}$), ~823 ($\nu_{C\text{-}H\ aro.}$); UV-Vis: λ_{max} (nm, DMSO): 341, 420; MS (+ES-MS): m/z = 488.48 (512) $(M + Na)^+$; Anal. Calc. (Found): $C_{28}H_{24}O_8$; C, 68.85 (68.88); H, 4.95 (4.91%).

General Procedure for Preparation of Various Hydroxy Substituted 1,7-bis(4-hydroxy, 3-methoxyphenyl)-1,6-heptadiene-3,5-bis-thiosemicarbazones (5,6,7)

The methanolic solutions of Knoevenagel condensates (**2–4**) (1 mmol) were reacted with thiosemicarbazide (2 mmol) with continuous stirring and addition of catalytic amounts of piperidine (0.05 cm^3) over 5–10 min. The reaction mixture was further stirred for 24 hrs and set aside when a dark brown solid precipitated out. The compound was purified by

recrystallization from chloroform-methanol to yield pure dark brown thiosemicarbazonates of Knoevenagel condensates.

4-Salicylidene-1,7-bis(4-hydroxy, 3-methoxyphenyl)-1,6-heptadiene-3,5-dithiosemicarbazone (5). Yield: 82%, mp: 108–110°C, ^{1}H-NMR ($CDCl_3$): δ 2.63 (s, 4H, NH_2 br), 3.78 (s, 6H, OCH_3), 6.6 (s, 2H, NH br), 6.84 (m, 14H, ArH), 8.00 (s, 1H, =CH-Ar); IR (KBr, cm^{-1}): ~3500 ($\nu_{O\text{-}H\ br.}$), ~3349 ($\nu_{N\text{-}H}$), ~3244, 3156 ($\nu_{C\text{-}NH2}$), ~3035, 2949 ($\nu_{=C\text{-}H,\ C\text{-}H}$), ~1610 ($\nu_{C=N}$), ~1502 ($\nu_{C=C}$), ~1367, 1028 ($\nu_{C\text{-}H}$), ~943 ($\nu_{H\text{-}C=C\text{-}Htrans}$), ~823.5 ($\nu_{C\text{-}H\ aro.}$), ~870 ($\nu_{C=S}$); UV-Vis: λ_{max} (nm, DMSO): 332, 410; MS (+ES-MS): m/z = 618.72 (620) (M + 1); Anal. Calc. (Found): $C_{30}H_{30}N_6O_5S_2$; C, 58.24 (58.29); H, 4.89 (4.84); N, 13.58 (13.52%).

4-(2,3-dihydroxy benzyl)-1,7-bis(4-hydroxy, 3-methoxyphenyl)-1,6-heptadiene-3,5-dithiosemicarbazone (6). Yield: 68%, mp: 127–129°C, ^{1}H-NMR ($CDCl_3$): δ 3.14 (s, 4H, NH_2 br), 3.85 (s, 6H, OCH_3), 6.8 (s, 2H, ArH), 7.1 (s, 2H, NH br), 7.4 (m, 7H, ArH), 7.99 (s, 1H, =CH-Ar), 6.33 (d, 2H, J=15.61 Hz, =C-H), 7.6 (2H, d, J=15.5 Hz, H-C=); IR (KBr, cm^{-1}): ~3751 ($\nu_{N\text{-}H}$), ~3553 ($\nu_{O\text{-}H\ br.}$), ~3289, 3164 ($\nu_{C\text{-}NH2}$), ~3009, 2943 ($\nu_{=C\text{-}H,\ C\text{-}H}$), ~1596 ($\nu_{C=N}$), ~1514 ($\nu_{C=C}$), ~1379, 1028 ($\nu_{C\text{-}H}$), ~945 ($\nu_{H\text{-}C=C\text{-}Htrans}$), ~817 ($\nu_{C\text{-}H\ aro.}$), ~874 ($\nu_{C=S}$); UV-Vis: λ_{max} (nm, DMSO): 322, 403; MS (+ES-MS): m/z = 634.72 (636) (M + 1); Anal. Calc. (Found): $C_{30}H_{30}N_6O_6S_2$; C, 56.77 (56.81); H, 4.76 (4.73); N, 13.24 (13.30%).

4-(3,4-dihydroxy benzyl)-1,7-bis(4-hydroxy, 3-methoxyphenyl)-1,6-heptadiene-3,5-dithiosemicarbazone (7). Yield: 79%, mp: 132–134°C, ^{1}H-NMR ($CDCl_3$): δ 2.96 (s, 4H, NH_2 br), 3.87 (s, 6H, OCH_3), 6.56 (s, 2H, NH br), 6.88 (dd, 4H, J = 8.2 Hz, ArH, J = 16.01 Hz, H-C=), 7.04 (s, 2H, ArH), 7.49 (m, 5H, ArH), 6.2 (d, 2H, J = 15.67 Hz, =C-H), 8.0 (s, 1H, =CH-Ar); IR (KBr, cm^{-1}): ~3683 ($\nu_{N\text{-}H}$), ~3617 ($\nu_{O\text{-}H\ br.}$), ~3262, 3155 ($\nu_{C\text{-}NH2}$), ~3012, 2949 ($\nu_{=C\text{-}H,\ C\text{-}H}$), ~1610 ($\nu_{C=N}$), ~1517 ($\nu_{C=C}$), ~1380, 1026 ($\nu_{C\text{-}H}$), ~945 ($\nu_{H\text{-}C=C\text{-}Htrans}$), ~844 ($\nu_{C\text{-}H\ aro.}$), ~869 ($\nu_{C=S}$); UV-Vis: λ_{max} (nm, DMSO): 326, 404; MS (+ES-MS): m/z = 634.72 (635.5) (M + 1); Anal. Calc. (Found): $C_{30}H_{30}N_6O_6S_2$; C, 56.77 (56.73); H, 4.76 (4.72); N, 13.24 (13.28%).

General Procedure for Preparation of Copper(II) Conjugates of Hydroxy Substituted 1,7-Bis(4-hydroxy, 3-methoxyphenyl)-1,6-heptadiene-3,5-diones (8,9,10)

Copper(II) conjugates were prepared *in situ* by dissolving the Knoevenagel condensates (**2**–**4**) in methanol with dropwise addition of piperidine (0.05 cm^3) and methanolic solution of $CuCl_2 2 \cdot H_2O$ (1 mmol). The reaction mixture was stirred for the period of 3 hr. The light brown precipitate separated out was isolated by vaccum filtration, washed with cold methanol and dried overnight in vacuo at ambient temperature.

[4-Salicylidene-1,7-bis(4-hydroxy, 3-methoxyphenyl)-1,6-heptadiene-3,5-dione] copper(II) (8). Yield: 82%, IR (KBr, cm^{-1}): ~3453 ($\nu_{O\text{-}H\ br.}$), ~3110, 2949 ($\nu_{=C\text{-}H,\ C\text{-}H}$), ~1614 ($\nu_{C=O}$), ~1589 ($\nu_{C=C}$), ~1390, 1031 ($\nu_{C\text{-}H}$), ~829 ($\nu_{C\text{-}H\ aro.}$), ~551 ($\nu_{Cu\text{-}O}$), ~332 ($\nu_{Cu\text{-}Cl}$); UV-Vis: λ_{max} (nm, DMSO): 353, 465; Anal. Calc. (Found): $C_{28}H_{24}Cl_2CuO_7$; C, 55.41 (55.62); H, 3.99 (4.12); Cu, 10.47 (10.38%).

[4-(2,3-dihydroxy benzyl)-1,7-bis(4-hydroxy, 3-methoxyphenyl)-1,6-heptadiene-3,5-dione] copper(II) (9). Yield: 87%, IR (KBr, cm^{-1}): ~3479 ($\nu_{O\text{-}H\ br.}$), ~3018, 2945 ($\nu_{=C\text{-}H,\ C\text{-}H}$), ~1591 ($\nu_{C=O}$), ~1506 ($\nu_{C=C}$), ~1406, 1028 ($\nu_{C\text{-}H}$), ~827 ($\nu_{C\text{-}H\ aro.}$), ~559 ($\nu_{Cu\text{-}O}$), ~336 ($\nu_{Cu\text{-}Cl}$); UV-Vis: λ_{max} (nm, DMSO): 335, 476, 506 ($dd_{trans.}$); Anal. Calc. (Found): $C_{28}H_{24}Cl_2CuO_8$; C, 53.99 (54.12); H, 3.88 (3.96); Cu, 10.20 (10.34%).

[4-(3,4-dihydroxy benzyl)-1,7-bis(4-hydroxy, 3-methoxyphenyl)-1,6-heptadiene-3,5-dione] copper(II) (10). Yield: 81%, IR (KBr, cm^{-1}): ~3544 ($\nu_{O\text{-}H\ br.}$), ~3026, 2941 ($\nu_{=C\text{-}H,\ C\text{-}H}$), ~1587 ($\nu_{C=O}$), ~1525 ($\nu_{C=C}$), ~1357, 1026 ($\nu_{C\text{-}H}$), ~823 ($\nu_{C\text{-}H\ aro.}$), ~555 ($\nu_{Cu\text{-}O}$), ~331 ($\nu_{Cu\text{-}Cl}$); UV-Vis: λ_{max} (nm, DMSO): 398, 509 ($dd_{trans.}$); Anal. Calc. (Found): $C_{28}H_{24}Cl_2CuO_8$; C, 53.99 (54.21); H, 3.88 (4.07); Cu, 10.20 (10.11%).

General Procedure for Preparation of Copper(II) Conjugates of Hydroxy Substituted 1,7-Bis-(4-hydroxy,3-methoxyphenyl)-1,6-heptadiene-3,5-dithiosemicarbazones (11,12,13)

The copper(II) conjugates were prepared by interaction of the methanolic solutions of Schiff bases of Knoevenagel condensate (**8**–**10**) (1 mmol) with $CuCl_2 \cdot 2H_2O$ (1 mmol) in presence of catalytic amount of piperidine (0.05 cm^3). The separated light brown precipitates were isolated after 3 hr of continuous stirring and washed with cold methanol. They were dried overnight in vacuo at ambient temperature.

[4-Salicylidene-1,7-bis(4-hydroxy, 3-methoxyphenyl)-1,6-heptadiene-3,5-dithiosemicarbazone] copper(II) (11). Yield: 78%, IR (KBr, cm^{-1}): ~3575 ($\nu_{O\text{-}H\ br.}$), ~3215, 3126 ($\nu_{C\text{-}NH2}$), ~3012, 2941 ($\nu_{=C\text{-}H,\ C\text{-}H}$), ~1593 ($\nu_{C=N}$), ~1508 ($\nu_{C=C}$), ~1360, 1028 ($\nu_{C\text{-}H}$), ~815 ($\nu_{C\text{-}H\ aro.}$), ~856 ($\nu_{C=S}$), ~435 ($\nu_{Cu\text{-}N}$), ~350 ($\nu_{Cu\text{-}S}$); UV-Vis: λ_{max} (nm, DMSO): 306, 459; Anal. Calc. (Found): $C_{30}H_{30}CuN_6O_5S_2$; C, 52.81 (53.13); H, 4.43 (4.27); N, 12.32 (12.48), Cu, 9.31 (9.54%).

[4-(2,3-dihydroxy benzyl)-1,7-bis(4-hydroxy, 3-methoxyphenyl)-1,6-heptadiene-3,5-dithiosemicarbazone] copper(II) (12). Yield: 83%, IR (KBr, cm^{-1}): ~3607 ($\nu_{O\text{-}H\ br.}$), ~3264, 3154 ($\nu_{C\text{-}NH2}$), ~3030, 2947 ($\nu_{=C\text{-}H,\ C\text{-}H}$), ~1575 ($\nu_{C=N}$), ~1514 ($\nu_{C=C}$), ~1369, 1028 ($\nu_{C\text{-}H}$), ~817 ($\nu_{C\text{-}H\ aro.}$), ~867 ($\nu_{C=S}$), ~441 ($\nu_{Cu\text{-}N}$), ~345 ($\nu_{Cu\text{-}S}$); UV-Vis: λ_{max} (nm, DMSO): 329, 395, 515 ($dd_{trans.}$); Anal. Calc.

(Found): $C_{30}H_{30}CuN_6O_6S_2$; C, 51.60 (51.09); H, 4.33 (4.78); N, 12.04 (12.18), Cu, 9.10 (9.22%).

[4-(3,4-dihydroxy benzyl)-1,7-bis(4-hydroxy, 3-methoxy-phenyl)-1,6-heptadiene-3,5-dithiosemicarbazone] copper(II) (13). Yield: 79%, IR (KBr, cm^{-1}): ~3692 ($\nu_{O\text{-}H\ br.}$), ~3249, 3077 ($\nu_{C\text{-}NH2}$), ~3019, 2943 ($\nu_{=C\text{-}H,\ C\text{-}H}$), ~1600 ($\nu_{C=N}$), ~1517 ($\nu_{C=C}$), ~1359, 1026 ($\nu_{C\text{-}H}$), ~814 ($\nu_{C\text{-}H\ aro.}$), ~856 ($\nu_{C=S}$), ~448 ($\nu_{Cu\text{-}N}$), ~352 ($\nu_{Cu\text{-}S}$); UV-Vis: λ_{max} (nm, DMSO): 395, 473, 557 ($dd_{trans.}$); Anal. Calc. (Found): $C_{30}H_{30}CuN_6O_6S_2$; C, 51.60 (51.78); H, 4.33 (4.51); N, 12.04 (12.26), Cu, 9.10 (9.28%).

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