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Synthesis and Physico-Chemical Characterizations of Novel Hydrazone Ligands and Their Metal Complexes against Hormone-Dependent and Independent Cancers

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Abstract

This work deals with the synthesis and physicochemical characterizations of a new group of novel retinoidal ligands and their metal complexes. Their *in vitro* anti-proliferative activities have shown that ligand **L1** is effective against human breast cancer BT-20 and MCF-7 cell lines. At the same time, compound **L2** exerts its effect on human prostate cancer PC-3 and human breast cancer MDA-MB-231 and MCF-7 cell lines respectively. The retinoid ligands exert their pleiotropic action toward retinoic acid receptors (RARs) than their metal complexes but all compounds exhibit concentration-dependent.

Keywords

Metal Complexes, Cancers, Antioxidant, Hydrazone, Retinoid Receptors

1. Introduction

Retinoid is a term used to describe both naturally occurring forms of vitamin A and its analogs [1]. Retinoids have been shown to have multiple therapeutic benefits, such as inhibition of inflammation, keratinization [2], embryonic development, epithelial differentiation, and growth control [3]. Retinoids exert their pleiotropic action toward retinoic acid receptors (RARs) and retinoid x receptors (RXRs) which belong to nuclear receptors superfamily [4]. There are currently two orally administered retinoids in common use: isotretinoid and etretinate [2]. Chemically, the retinoids are defined as diterpenoids derived from a monocyclic parent compound containing five carbon-carbon double bonds

and a functional group at the terminus of the acyclic portion. However, this definition does not account for more potent, newer synthetic retinoids such as tri- or tetra-cyclic retinoidal benzoic acid derivatives, which may not be diterpenoids or may not be derived from the monocyclic parent compound. Structures of certain retinoids derived from monocyclic structures such as retinol or retinoic acid, as well as multicyclic structures such as retinoidal benzoic acid, can be modified to yield an almost unlimited number of retinoids [5]. During the past decade, more than a thousand retinoids and retinoid-like compounds with modified molecular structures have been synthesized and tested in a variety of animal and cell culture systems for their therapeutic effects both in dermatological diseases and neoplastic disorders [6]. However, to characterize the biological activity and toxicity of new retinoids an enormous number of *in vivo* and *in vitro* experiments have to be performed. Interestingly, almost of retinoids show low toxicity and play a key role in differentiation, proliferation, and apoptosis [7] [8] [9]. The description above prompted us to study by focusing on synthetic compounds with improved more effective retinoids for modulating cell differentiation and proliferation against human estrogen-independent breast cancer cell lines (BT-20 and MDA-MB-231) and human estrogen-dependent breast cancer cell lines (MCF-7).

2. Experimental

2.1. Chemical Materials

All chemical materials employed in the present work were purchased from Aldrich Chemicals (USA). All solvents were used of AR grade and were purified by standard method before use.

2.2. Physical Measurements

Infrared spectra were recorded with Infrared spectra were recorded as KBr disc on a Perkin Elmer 283-B infrared spectrophotometer. The analysis of C, H, and N components of the compounds and their metal complexes was performed on CHNS/O ANALYSER (Perkin Elmer PE2400 Series II). Electronic absorption spectra were recorded on Spectronic Genesys-2 and Perkin-Elmer Lambda 20 UV-VIS spectrophotometer using a matched pair of 1 cm quartz cells. Electrochemical properties were measured in DMSO solvent on BAS CV-27 instrument in conjunction with X-Y recorder using a three-compartment cell consisting of the platinum working electrode, a platinum wire as an auxiliary electrode, and saturated calomel as a reference electrode (SCE) with 0.1 M TEAP as a supporting electrolyte in our laboratory. Magnetic susceptibilities of their metal complexes were measured at 300 K on a Faraday balance having a field strength of 7000 KG by using $Hg[Co(SCN)_4]$ as a calibrant and ESR studies were carried out in Electron Spin Resonance Model JES-RE2X, Jeol, Japan, Microwave: X-Band, using Mn^{2+} Marker as a standardization.

2.3. Antioxidant Activity by DPPH Method

The assay was performed as described by Sharma *et al.* [10], and the DPPH radical scavenging activity of the compounds was measured. Briefly, 0.2 mM of 2,2-Diphenyl-1-picrylhydrazyl (DPPH) solution was prepared with a methanolic solvent. 100 µL sample was added to 3.9 cm^3 DPPH solution and was incubated in the dark for 30 min at a temperature of 37˚C then the absorbance was measured at λ_{max} 517 nm, calculating the percentage of anti-free radical activities.

2.4. Antioxidant Activity by FRAP Method

Prepare FRAP (ferric reducing/antioxidant power) by preparing acetate buffer pH 3.6, 10 mM TPTZ (2,4,6-tris(2-pyridyl-s-trizine)) in solution 40 mM of HCl, and 20 mM of ferric chloride and then mix at the proportion of 10:1:1 (v/v). This will get FRAP solution, then prepare sample solution in purified water with the required concentrations [10].

2.5. Antiproliferative Activities to Cancer Cell Lines

The breast (MCF-7, MDA-MB-231, BT-20) and prostate (PC-3) cancer cell lines during growth stage (9×10^4 cell/mL) 45 µL. Add sample element 5 µL diluted by DMSO 5% mixed with 384-well plated and incubate at a temperature of 37˚C with 5% of CO_2 for 3 days, then add solution resazurin 62.5 µg/mL 12.5 µL, incubate 4 hours at a temperature of 37˚C. Then draw a graph for the relation between the concentration and the value of the response of cell inhibition [11] [12] [13].

2.6. Statistical Analysis

All determinations of samples were determined in triplicate and mean values were reported for each case along with standard deviation (±SD). The antioxidant activities of the compounds were by ANOVA one-way test, using SPSS program ($p < 0.05$).

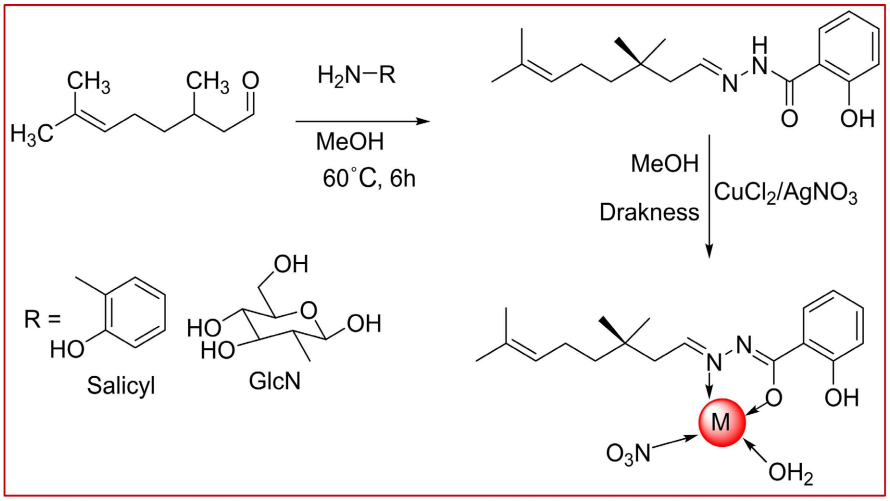
3. Synthesis

3.1. Synthesis of Ligands (L1, L2)

Ligands were synthesized by interacting of (3R)-(+)-citronellal with hydrazide by mole ratio 1:1 in MeOH at 60˚C for 6 h as in Scheme 1. The corresponding compound was filtrated and dried properly in vacuo. The compounds yielded 80% for L1 and 95% for **L2**, respectively. [**L1** Found C 60.75, H 8.23, N 4.45, O 25.38; $C_{16}H_{29}NO_5$ calc C 60.88, H 9.19, N 4.44, O 25.36, i.r. spectra (KBr disc): 3228 cm^{-1} ν(N-H), 1658 cm^{-1} ν(C=O), 1550 cm^{-1} ν(C=N)]. [**L2** Found C 70.83, H 8.33, N 9.72, O 5.55; $C_{17}H_{24}N_2O$ calc C 70.74, H 8.32, N 9.71, O 5.55, i.r. spectra (KBr disc): 3265 cm^{-1} ν(N-H), 1647 cm^{-1} ν(C=O), 1537cm^{-1} ν(C=N)].

3.2. Synthesis of Metal Complexes (C1-C4)

Metal complexes were synthesized using an identical procedure as shown in



Scheme 1. General synthetic scheme for preparation of citronellal hydrazones (L1, L2) and their metal complexes (C1-C4).

Scheme 1. Copper (II) chloride dihydrate was added to citronellal hydrazone in methanol solvent at a proper stoichiometry in molar ratio 1:1. The product was separated by centrifugation and dried in a vacuum. The reaction was carried out in darkness and without heating for 3 h. The products were gained 67% for **C1**, 73% for **C2**, 75% for **C3**, 70% for **C4**, respectively. [**C1** Found C 44.45, H 7.20, N 3.32, O 20.35, Cu 14.65; $Cu(C_{16}H_{29}NO_5(H_2O)Cl)$ calc C 44.40, H 7.17, N 3.24, O 20.22, Cu 14070; i.r. spectra (KBr disc): 1525 $cm^{-1}\nu$ (C=N), 1616 cm^{-1} ν(C=N-N=C), 1373 cm^{-1} ν(C-O)]. [**C2** Found C 50.30, H 6.82, N 6.87, O 7.80, Cu 15.70; $Cu(C_{17}H_{24}N_2O(H_2O)Cl)$ calc C 50.30, H 6.41, N 6.91, O 7.89, Cu 15.68; i.r. spectra (KBr disc): 1530 cm^{-1} ν(C=N), 1610 cm^{-1} ν(C=N-N=C), 1350 cm^{-1} ν(C-O)]. [**C3** Found C 38.25, H 6.20, N 5.63, O 28.59, Ag 21.45; $Ag(C_{16}H_{29}NO_5$-$(NO_3)(H_2O))$ calc C 38.15, H 6.16, N 5.56, O 28.61, Ag 21.43; i.r. spectra (KBr disc): 1635 cm^{-1} ν(C=N), 1615 cm^{-1} ν(C=N-N=C), 1370 cm^{-1} ν(C-O)]. [**C4** Found C 42.79, H 5.06, N 8.75, O 16.85, Ag 22.70; $Ag(C_{17}H_{24}N_2O(NO_3)(H_2O))$ calc C 42.83, H 5.04, N 8.82, O 16.80, Ag 22.65; i.r. spectra (KBr disc): 1638 cm^{-1} ν(C=N), 1615 cm^{-1} ν(C=N-N=C), 1372 cm^{-1} ν(C-O)].

4. Result and Discussions

4.1. Physicochemical Characterization of Samples

Physicochemical properties of compounds from synthesis, both ligands; Citronellal d-glucosamine hydrazone (L1) Citronellal salicylic hydrazone (L2), and complexes between ligands and metal ions (Cu^{2+} and Ag^{+}) are C1, C2, C3 and C4 produced from Scheme 1. All synthesized substances are polar compounds but polarity is high in ligands. These ligands are reacted with Lewis acid (copper and silver) to form C1, C2, C3, and C4 complexes with reduced polarity due to reduced charge. This is caused by the neutralization of negatively charged ligands with positively charged metal ions of copper and silver. The synthesized sub-

stances will have molecular weight, color, and soluble solvents as shown in Table 1.

Both ligands and complexes synthesized in this research showed high percentage yields by condensation reaction between natural aldehyde and hydrazide in a 1:1 mass stoichiometric ratio. From the study of chemical composition, it was found that complexes have a general formula as [M(ligand)(H_2O)(NO_3)/Cl], corresponding to our previous studies [11] [14] [15] and others [16] [17].

4.2. Electronic Spectroscopy

The electronic spectra of (3*R*)-(+)-citronellal hydrazones and their metal complexes are recorded in DMSO solvent. The complexes exhibit two bands and showed a blue shift compared with their ligands: one band in the region 10,627 - 13,459 cm^{-1}, and another band in the region 29,851 - 30,120 cm^{-1} region. The copper (II) complexes of these ligands showed moderate Jahn-Teller distortion the lowest energy transition $d_z^2 \rightarrow d_{x-y}^{22}\left({}^2B_{1g} \rightarrow {}^2B_{2g}\right)$ occurred in the 10,627 - 13,459 cm^{-1} similar to previously reported of Mandal *et al.* [18] [19]. However, the high-intensity bands observed at the lower wavelength region (29,851 - 30,120 cm^{-1}) are due to π-π* transition of the imino functionality [20].

4.3. Infrared Spectroscopy

The data show bands corresponding to the imide ν(N-H) and the keto ν(C=O) groups suggesting that in the solid state, the ligands exist in the keto form [21]. In spectra of complexes, the blue shift of imine ν(C=N) spectral bands of citronellal hydrazones from about (1537 - 1550 cm^{-1}) to (1525 - 1530 cm^{-1}) for the metal complexes indicating the coordination of the azomethine nitrogen and corresponding to ν(N=N) from (957 - 977 cm^{-1}) to (1024 - 1037 cm^{-1}) expected to reduce the electron density in the azomethine group and also the bands expected for ν(N-H) and ν(C=O) disappeared to produce new bands about (1610 - 1616 cm^{-1}) and (1350 - 1373 cm^{-1}) can determine for the characteristic of the azomethine [ν(C=N-N=C)] and ν(C-O) group, respectively. The coordination of azomethine nitrogen is confirmed with the presence of a new band at about 414 - 424 cm^{-1} and 532 - 553 cm^{-1} assignable to ν(Cu-N), ν(Cu-O) and 1638 cm^{-1}, 1372 cm^{-1} assignable to ν(Ag-N), ν(Ag-O), respectively. The presence of coordinated water molecules in the complexes of broad bands in the region about 3540 - 3350 cm^{-1} [22] [23] [24].

4.4. Magnetic Susceptibility and EPR Studied

The magnetic moment (μ_{eff}, BM) values of (3R)-(+)-citronellal hydrazone copper and silver complexes have shown in the range 1.70 - 1.75 B.M. as shown in Table 2. These values expected for square-planar ligation about the copper (II) ion is probable [25] and indicate them to be monomeric. For which the EPR spectra of compounds were recorded in DMSO solvent at liquid nitrogen

Table 1. Physicochemical properties of samples.

Trivial name	Code	MW	Color of samples	Solvents
Cit-D-Glu	L1	315.40	reddish brown	DMSO, DMF, MeOH, EtOH
Cit-Sal	L2	288.38	White	DMSO, DMF, MeOH, EtOH
Cit-D-Glu-Cu	C1	432.40	Green	DMSO, DMF, MeOH, EtOH
Cit-Sal-Cu	C2	405.37	Green	DMSO, DMF, MeOH, EtOH
Cit-D-Glu-Ag	C3	503.27	Black	DMSO, DMF, MeOH, EtOH
Cit-Sal-Ag	C4	476.25	Gray	DMSO, DMF, MeOH, EtOH

Table 2. Magnetic moment and EPR parameters of (3*R*)-(+)-citronellal hydrazonate copper complexes (C1-C2) and silver complexes (C3-C4).

Samples	μ_{eff} (BM)	$g_{//}$	$g_{\perp}$	$A_{//}$		f (cm)
				(mT)	($\times 10^{-4}$ cm^{-1})	
C1	1.72	2.42	2.07	15.6	176	137
C2	1.70	2.30	2.05	13.8	148	155
C3	1.75	2.51	2.07	16.5	165	145
C4	1.74	2.51	2.11	16.3	172	138

$g_{//} = g_{parallel}$, $g_{\perp} = g_{perpendicular}$.

temperature and these spectra showed a set of four well-resolved peaks at the low-field region and another weaker signal at the high-field region corresponding to $g_{//}$ and $g_{\perp}$, respectively. The observed $g_{//}$ values for citronellal hydrazone copper and silver complexes 2.30 and 2.51 suggest the presence of a small amount of ionic character of the metal-ligand bond. The $g_{//} > g_{\perp} > 2.0023$ were observed for these compounds plausible that the unpaired electron is localized in d^{22}_{x-y} orbital of the copper (II) ion [26] [27]. The axial symmetry parameter G is defined as $G = [g_{//} - 2.0023]/[g_{\perp} - 2.0023]$. The calculated G values for these compounds indicate that there are no magnetic interactions between the copper and silver centers in DMSO medium.

4.5. Cyclic Voltammetry of Complexes (C1-C4)

The cyclic voltammetric profile of citronellal hydrazonate metal complexes recorded in the range +1.0 and −1.5 V were given and the redox potentials of all compounds are summarized as shown in **Table 3**. All complexes show a redox couple in the +0.18 to +0.26 V ascribed to $Cu^{2+/1+}$ redox process. The different $\Delta E_p = E_{pc} - E_{pa}$ exceeds the Nernstain requirement of 0.059 V suggesting that all of them showed the reversible character and the anodic to cathodic peak current ratio (i_{pa}/i_{pc}) is equal to unity even though the scan rate was varied between 100

Table 3. Electrochemical data on metal complexes of (3*R*)-(+)-citronellal hydrazonates at 298 k[a].

Compound	E_{pc}(v)	E_{pa}(v)	$E_{1/2}$	E_{pc}/E_{pa}	ΔE_p
C1	+0.16 −0.98	+0.20	+0.18	0.90	0.07
C2	+0.21 −0.58	+0.30 −0.43	+0.26	0.92	0.09
C3	−0.09 −0.29	−0.15 −0.48	+0.70	0.60	0.06
C4	−0.10 −0.30	−0.17 −0.47	+0.69	0.58	0.07

[a]In DMSO solvent.

and 300 mVs^{-1} which indicate the chemical reversibility of the redox nature change of the metal redox couple for complexes. An irreversible one-electron reduction wave at *ca.* −0.58 to −0.98 V of these compounds is attributable to the $Cu^{1+/0}$ reduction [28]. The facile interconversions of the $Cu^{2+/1+}$ valencies observed for the present complexes might be relevant to the biological activities of copper complexes [29].

4.6. Biological Activities

Antioxidant activity: The ability of anti-free radical activities by using the DPPH and FRAP methods. The calculation of the inhibitory concentration 50% is illustrated in **Table 2**. It is found that the novel Schiff base ligands anti-free radical DPPH at a high percentage. All compounds showed anti-free radical DPPH and also showed a concentration dependence on both ligands and their metal complexes but hydrazonate metal complexes have lower proficiency than independent ligands because of the bigger structure resulting in the steric effect that makes it difficult to provide hydrogen-free radical. For anti-free radical activity by reducing Fe^{3+} to Fe^{2+} (FRAP). It is found that ligands and their complexes showed low ability to reduce iron because the molecule has difficulty in providing single electron transfer. Antioxidants have a differing capacity to stop the propagation of free radicals, influencing this both the structure of the antioxidant and the structure of the compounds to be oxidized [30] [31].

Many chemopreventive agents, *viz.* retinoids and anti-estrogens, are believed to block or delay the progression of transformed cells by modulating cell proliferation or differentiation [32] [33]. Retinoids including classical and non-classical retinoids have been shown to modulate cellular growth and differentiation of normal and neoplastic epithelial cells by interacting with nuclear receptors that function as retinoid-dependent transcription factors [34] [35] [36]. Although classical retinoids viz. all-*trans*-retinoic acid (ATRA) possess apoptosis induction this effect is weak and is only seen when these compounds are used at supraphysiological concentrations and long-term use shows adverse side effects and resistances [8]. Certain synthetic retinoid-related molecules (non-classical retinoids) were developed with low toxicity and exert high potency for anticancer

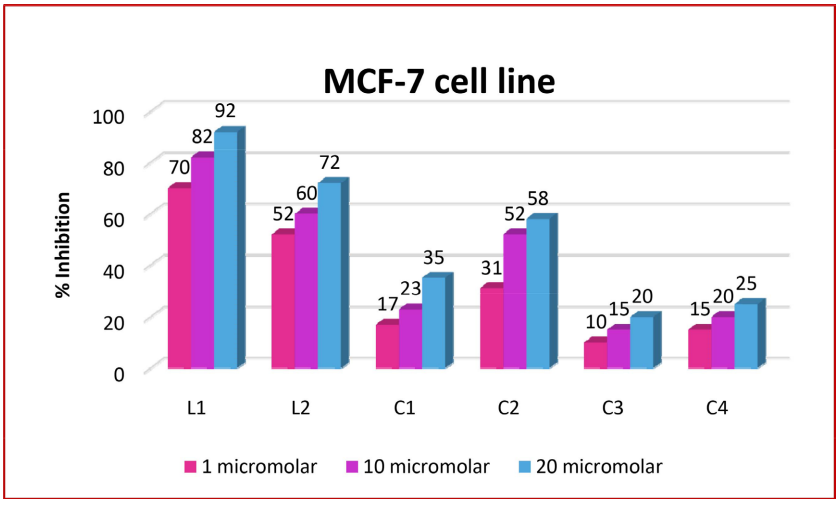


Figure 1. Antiproliferative effects of citronellal hydrazone (L1, L2) and their metal conjugates (C1-C4) against MCF-7 (RAR*α*, *β*).

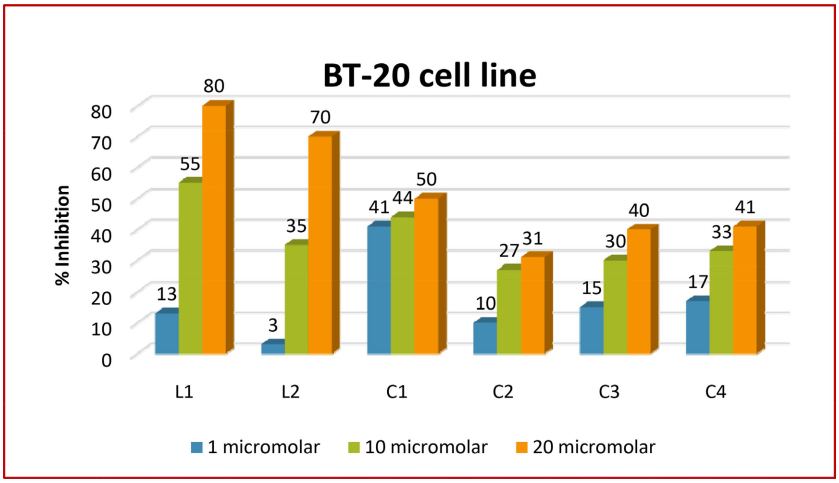


Figure 2. Antiproliferative effects of citronellal hydrazone (L1, L2) and their metal conjugates (C1-C4) against BT-20 (RAR*α*).

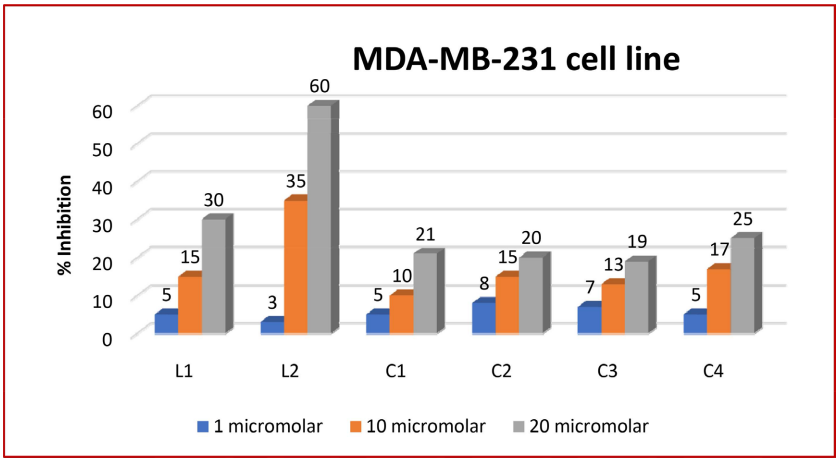


Figure 3. Antiproliferative effects of citronellal hydrazone (L1, L2) and their metal conjugates (C1-C4) against MDA-MB-231 (RAR*γ*).

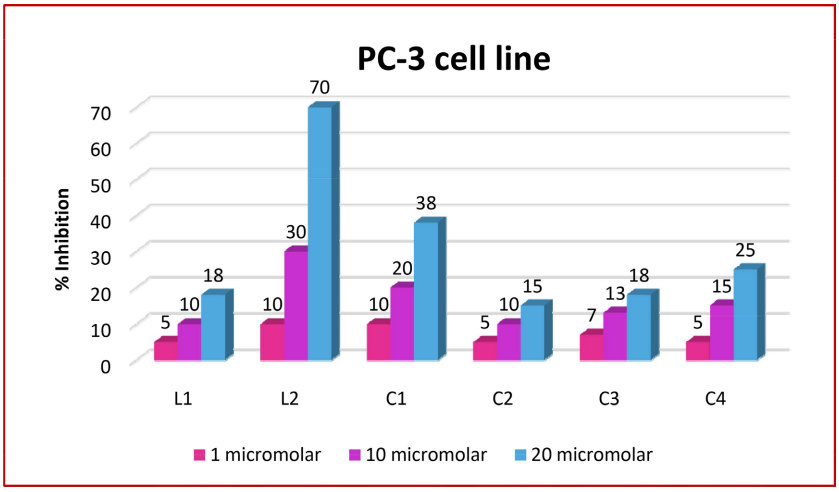


Figure 4. Cell growth inhibition by citronellal hydrazone (L1, L2) and their metal conjugates (C1-C4) against human prostate cancer (PC-3) cell line.

agents urgently needed. In the present work, six such compounds have been evaluated against human estrogen-dependent breast cancer cell line (MCF-7) and estrogen-independent breast cancer cell lines (BT-20 and MDA-MB-231) as shown in **Figure 1**, **Figure 2**, and **Figure 3** as well as human androgen-insensitive prostate cancer (PC-3) cell line as shown in **Figure 4**, respectively.

On breast cancer cell lines: Both ligands (**L1** and **L2**) exhibit enhanced inhibitory activity against both ER+ve (MCF-7) and ER-ve (BT-20) cell lines indicating their preferential action on the cancer cells. When analyzed in terms of the sub-type selectivity it becomes apparent that these compounds probably have some preferences for RARα, β sub-type. As a result, they fail to exhibit any inhibition against ER-ve MDA-MB-231 cells having RARγ status. Unfortunately, metal conjugation does not seem to contribute to the enhancement of the activity.

On prostate cancer cell lines: Almost all compounds show considerably less sensitivity to PC-3 (androgen receptor-independent) cell line except the compound L2 although metal conjugation effects are not necessarily consistent.

5. Conclusion

Present work thus reveals that citronellal hydrazones are potent inhibitors against ER+ ve as well as ER-ve breast cancer cell lines. Their action is, however, independent of estrogen receptor status. The compounds are also effective against androgen receptor-independent prostate cancer cells giving credence to the importance of retinoid receptors as targets for designing effective antitumor compounds.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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