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Synthesis, characterization, in-vitro antibacterial and anticancer studies on some metal(II) complexes of (methylsulfanyl)chromenol Schiff base

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ABSTRACT

Mn(II), Co(II), Ni(II), Cu(II) and Pd(II) complexes of the Schiff base, 6-methyl-3-[[4-(methylsulfanyl)phenyl]imino}methyl]-3,4-dihydro-2*H*-chromen-4-ol are synthesized and characterized by microanalysis, conductance, ^{1}H NMR, infrared and electronic spectral measurements. The ligand coordinates through the chromenol *O* and imine *N* atoms to the metal ions, and the Co(II) and Ni(II) complexes are in the trans-isomeric form as shown by IR measurements. All the complexes form as $[ML_2]xH_2O$ with the exception of the Mn(II) complex which analyzed as $[MLNO_3]H_2O$. Electronic measurements are indicative of a four coordinate, tetrahedral /square-planar geometry for the complexes and none is an electrolyte in nitromethane. The antibacterial studies reveal that the Schiff base and its Cu(II) complex exhibit broad-spectrum antibacterial activity against *Proteus mirabilis*, *Escherichia coli* and *Staphylococcus aureus* with inhibitory zones range of 11.0-13.0 mm and 10.0-16.0 mm respectively. The cytotoxic study shows that the Cu(II) complex has the best in-vitro anticancer activity against both HT-29 (colon carcinoma) and MCF-7(human breast adenocarcinoma) cells with activities of about a half (17.02 µM), and a fifth(9.78 µM) that of Cis-platin respectively.

Introduction

Chromenyl Schiff base and chelates are associated with lots of bioactivities such as antibacterial, antifungal and anticancer .e.g. Cu(II), Ni(II) and Cu(II) chelates of the Schiff base derived from aminoantipyrine and 3-formyl chromone exhibited good in-vitro antibacterial activity against *S. aureus*, *E. coli* and *P. aeuriginosa* [1], and various (thiomethyl)anilines are used as fungicide in agriculture against *Venturia inaequalis* infections in apple seedlings [2]. In addition, Schiff bases derived from 3-formyl chromone/6-methyl-3-formyl chromone and various sulfonamides(homo sulfanilamide and 4-aminoethylbenzene sulfonamide) and their Zn(II) complexes exhibited inhibitory activities against tumor-associated carbonic anhydrase isozymes [3], while those derived from 4-anilo-5H-pyridazino(4,5-b) indoles and 2-furanmethanethiol are potent anticancer agent against Bel-7402(human liver cancer, hepatoma) and HT-1080(human fibrosarcona) [4]. Furthermore, the mixed Schiff base derived from mercaptobenzothiazole, formalin and phenylamine are corrosion inhibitors [5]. Extensive literature search reveals that no information is available on the Schiff base, 6-methyl-3-[[4-(methylsulphanyl) phenyl]imino}methyl]-3,4-dihydro-2*H*-chromen-4-ol (derived from condensation of 3-formyl-6-methylchromone and 4-methylthio aniline) and its Mn(II), Co(II), Ni(II), Cu(II) and Zn(II) complexes [6-10]. Thus, the aims are to Synthesize, characterize and investigate the in-vitro antibacterial and anticancer properties of the above named Schiff base and its metal(II) complexes for further studies as antiseptics, and lead compounds in drug research for breast and colon carcinomas. The ligand and its metal (II) complexes are new and are reported here for the first time as a continuation of our studies on the Synthesis, characterization and bioactivities of some metal(II) complexes of various Schiff bases [11-15].

Experimental

Reagent grade 3-formyl-6-methylchromone and 4-methylthioaniline (Aldrich), hydrated cobalt(II) nitrate, nickel(II) nitrate, copper(II) nitrate and manganese(II) nitrate, and palladium(II) chloride (BDH chemicals) are used as received and the solvents are purified by distillation.

Synthesis of the ligand

The ligand, *6-methyl-3-[[4-(methylsulphanyl)phenyl]imino}methyl]-3,4-dihydro-2H-chromen-4-ol*, is prepared by adding 7.97 mmol (1.10 g) of 4-methylthioaniline in 20 mL of absolute ethanol drop wise to a stirring hot 30 mL ethanolic solution of 7.97 mmol (1.50 g) of 3-formyl-6-methylchromone at 60^0C. The resulting homogeneous yellow solution is then refluxed for 6 h after the addition of 6 drops of acetic acid. The yellow product, formed on cooling in ice, is filtered and recrystallized from ethanol and dried *in vacuo* over anhydrous calcium chloride. The yield of the resulting Schiff base (Figure 1) is 1.73 g (70 %). ^{1}H nmr (ppm) δ 10.5(s, 1H, C^4 OH), 8.83(s, 1H, C^5), 8.07(m, 2H, C^7, C^8), 7.75(s, 1H, HCN), 7.45 (m, 4H, $C^{2'}$ $C^{3'}$, $C^{6'}$), 2.48 (s, 3H(CH_3S), $C^{4'}$), 2.35 (s, 3H(CH_3), C^6), 1.24(s, 2H,C^2).

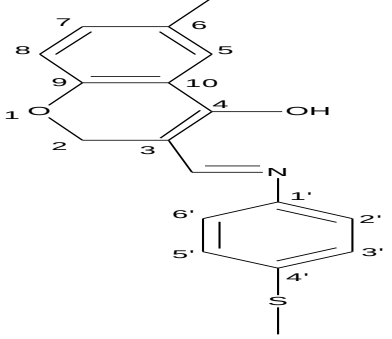

Fig 1 Structural formula for the ligand

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Preparation of the Metal(II) Complexes

The various complexes are prepared by refluxing a homogeneous solution of 0.30 mmol (0.053-0.089 g) of hydrated M(II) nitrates (M = Co, Ni, Cu, Zn) and 0.60 mmol (0.19 g) of the ligand to which 0.06 mmol (0.061 g) of triethylamine is added in 30 mL of ethanol for 6 h. The products formed on cooling in ice are filtered, washed with ethanol, and dried *in vacuo* over anhydrous calcium chloride. Similar procedure is used to isolate the Pd(II) complex from its chloride.

Biological Studies

The antibacterial tests are done at the Department of Microbiology, University of Ibadan, Ibadan, Nigeria while the anticancer tests are carried out at the Institute of Medicinal and Pharmaceutical Chemistry, Technical University Braunschweig, Beethovenstrasse, 55, 38106 Braunschweig, Germany.

Antimicrobial assay

The assay is carried out on the ligand and its metal(II) complexes using the Agar diffusion technique. The surface of the Muller Hinton's agar in a Petri dish is uniformly inoculated with 0.3 mL of 18 hour old *Escherichia coli, Staphylococcus aureus, Klebsiella pneumoniae* and *Proteus mirabilis* culture. Using a sterile cork borer, 7 mm wells are bored into agar. Thereafter 10 mg/mL concentration of each metal complex in DMF is then introduced into the wells and the plates are allowed to stand on bench for 30 min before incubation at 37^0C for 24 h, after which inhibitory zones (in mm) are taken as a measure of antimicrobial activity. The experiments are conducted in duplicates with Sulfamethoxazole as the reference drug.

Cytotoxicity assay

The MCF-7 (human breast adenocarcinoma) and HT-29 (colon carcinoma) cells are maintained in minimum essential medium (MEM) supplemented with 10% of fetal caw serum (FCS), and 25 mg of gentamycin at 37^oC in a humidified atmosphere with 5% CO_2. In 96 well plates, 100 mL of a cell suspension in culture medium at 7500 cells/mL (MCF-7) and 2500 cells/ml (HT-29) are plated into each well and incubated for three days under culture conditions. After the addition of various concentrations of the test compounds, cells are incubated for another 96 h and 72 h respectively. Then the medium is removed and the cells are fixed with glutardialdehyde solution 1% and stored under phosphate buffered saline (PBS) at 4^OC. Cell biomass is determined by a crystal violet staining, followed by extracting of the bound dye with ethanol and a photometric measurement at 590 nm. Mean values are calculated and the effects of the compounds are expressed as % Treated/$Control_{corr}$ values according to the following equations:

T/C_{corr} [%] = (T-C_0/C-C_0).100

(C_0 is the biomass of control cells at the time of compound addition; C is the biomass of control cells at the time of the test end; T is the biomass of probes/samples at the time of the test end). The test compounds are prepared fresh as stock solutions in DMF and diluted with the cell culture medium to the final assay concentrations (0.1% v/v DMF) and Cis-platin is used as the reference drug. The IC_{50} value is determined as the concentration causing 50% inhibition of cell proliferation [16].

Physical Measurements

The electronic spectra are recorded on a Perkin-Elmer λ25 spectrophotometer while infrared spectra are done with Thermo Nicolet FTIR 200 spectrophotometer in the range 4000-400 cm^{-1} as KBr discs. The ^{1}H nmr spectrum is recorded on a 300 MHz Brucker DRX-400 NMR instrument in $CDCl_3$ at 295K, and ^{1}H chemical shifts are referenced to the residual signals of the protons of $CDCl_3$ and are quoted in ppm. The elemental analyses for C, H and N are recorded on Thermo Quest CE Instruments flash EA1112 analyser, while cobalt, nickel, copper, zinc and palladium are determined titrimetrically [17]. Electrolytic conductivities in nitromethane are determined using a HANNA HI 991300 conductivity meter and melting points (uncorrected) are done with Mel-Temp electro thermal machine.

Results and Discussion

The formation of ligand is confirmed by microanalysis and 1HNMR measurements. All the complexes adopt $[ML_2]xH_2O$ stoichiometry with the exception of the Mn(II) complex which analyzed as $[MLNO_3]H_2O$, and the Co(II) complex is hygroscopic. The generalized equation for the formation of the complexes is:

$$M(NO_3)_2\cdot 6H_2O + 2HL \rightarrow [ML_2]aH_2O + 2HNO_3 + bH_2O$$

(When M = Ni(II)/Cu(II){a = 3, b= 3})

The analytical data, colors, percentage yields, melting points, molar conductivities, and room temperature magnetic moments of the complexes are presented in Table 1. Attempts to isolate suitable crystals for single X-ray structural determination are not successful.

Conductance measurements

The molar conductivities of the complexes in nitromethane are in the range 10.0-18.0 ohm^{-1} cm^2 mol^{-1}, showing that they are non-electrolytes in the solvent. A value of 94.0-105.0 ohm^{-1} cm^2 mol^{-1} is expected for a 1:1 electrolyte [18].

Infrared and Electronic Spectra

The relevant infrared data are presented in Table 2. The band at 3417 cm^{-1} in the ligand is assigned as νOH and its broadness is attributed to intramolecular hydrogen bonding [19]. The absence of this band in the complexes indicates the involvement of the chromenol *O* in bonding to the metal ions. The new broad band at 3500 cm^{-1} in the complexes is assigned to ν(OH) of crystallization water. The uncoordinated C=N vibrations in the ligand are observed as four bands in the range 1650-1556 cm^{-1}. These bands are observed as three to four bands in the complexes with the exceptions of the Co(II) and Ni(II) complexes which have two bands and are bathochromic shifted to 1644-1501 cm^{-1}, confirming the involvement of the imine *N* atom in coordination to metal(II) ion. Moreover, it has been documented that some metal(II) Schiff base complexes do exhibit geometric isomerism [20], with the trans-isomer having two *ν*C=N bands, and the cis-isomer a lone *ν*C=N band. Thus, the Co(II) and Ni(II) complexes in this study have two *ν*C=N bands and are consequently in the trans-isomeric form (Figure 2). The δC—H vibration of the ligand is observed at 981 cm^{-1} and it suffers a bathochromic shift to 826-775 cm^{-1} in the complexes due to the pseudo-aromatic nature of the complexes [21]. Further evidence of coordination is the appearance of the bands due to ν(M—O) and ν(M—N) in the complexes at 498-414 and 572-534 cm^{-1} respectively, these bands are absent in the ligand spectrum.

The electronic spectra are presented in Table 2. The ligand bands are observed at 25.20, 36.80 and 40.98 kK, and are assigned to n→π*, π→π* and CT transitions. These bands are bathochromic / hypsochromic shifted in the complexes to 25.51-28.02, 30.12-33.78 and 36.90-40.68 kK due to coordination [20]. The Mn(II) complex, shows two absorption bands at 14.01 and 25.32 kK respectively, consistent with a four-coordinate, tetrahedral geometry and are assigned to $^6A_1 \rightarrow {}^4E_1$ (ν_1) and $^6A_1 \rightarrow {}^4A_1$ (ν_2) transitions [22]. The Co(II) complex shows two absorption bands at 15.30 and 20.94 kK typical of a 4-

coordinate, tetrahedral geometry and are assigned to $^4A_2 \rightarrow {}^4T_1(F)$, ($\nu_2$) and $^4A_2 \rightarrow {}^4T_1(P)$, ($\nu_3$) transitions [23]. The Ni(II) complex has absorptions typical of a tetrahedral geometry at 14.71 and 20.04 kK assigned to $^3T_1(F) \rightarrow {}^3T_2$, ($\nu_2$) and $^3T_1(F) \rightarrow {}^3A_2$, ($\nu_3$) transitions [23]. The observance of two bands at 15.0 and 24.07 kK in the Cu(II) complex is indicative of square planar geometry with the assignment $^2B_{1g} \rightarrow {}^2A_{1g}$ and $^2B_{1g} \rightarrow {}^2E_{1g}$. since tetrahedral and octahedral Cu(II) complexes have single bands below and above 10.0 kK respectively [12].The Pd(II) complex is expectedly square-planar, with absorption bands at 15.39 and 25.0 kK, assigned to $^1A_{1g} \rightarrow {}^1B_{1g}$ and $^1A_{1g} \rightarrow {}^1E_{2g}$ transitions [21].

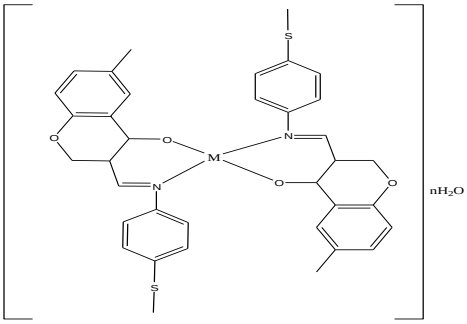

Fig 2 Proposed structure for the Ni(II) and Co(II) complexes

^{1}Hnmr spectra

The chromenol proton is observed at 10.5 ppm, while the imine proton is seen as a singlet at 7.75 ppm. The protons on C^5, C^7 and C^8 in the chromenol ring resonate as a singlet and multiplet at 8.83 and 8.07 ppm respectively. In addition, the protons at $C^{2'}$, $C^{3'}$, $C^{5'}$ and $C^{6'}$ in the methyl thio phenyl ring are observed as a multiplet at 7.45 ppm. The methyl group in thio phenyl ring is seen as a singlet 2.48 ppm while the methyl in chromenol ring is observed at 2.35 ppm. Finally, the 2H at C^2 resonate as a singlet at 1.24 ppm.

Antibacterial activity

The results of antibacterial activities are presented in Table 3 and shown in Figure 3. The ligand is active against Staphyloccous aureus, Esherichia coli and Proteus mirabilis with inhibitory zones range of 12.0-13.0 mm but it is inactive against Klebsiella pneumoniae, and the complexes are more susceptible to the gram negative bacteria due to their thin peptidoglycan layer, which makes it more permeable to the complexes [24]. Furthermore, none of the complex is active against Klebsiella pneumoniae, and all the metal complexes are active against Proteus mirabilis with inhibitory zones range of 11.0 -13.0 mm with the exception of the Pd(II) complex. The resistance of Klebsiella pneumoniae to the ligand and the metal complexes may be attributed to its ability to produce extended-spectrum beta-lactamases(ESBL)which inactivates the compounds [25]. The Mn(II) and Co(II) complexes are active against two organisms each .i. e. E. coli and P. mirabilis and S. aureus and P. mirabilis with inhibitory zones of 13.0 mm and 12.0 mm, and 9.0 mm and 12.0 mm respectively. Furthermore, the Ni(II) and Pd(II) complexes are active against P. mirabilis and E. coli only with inhibitory zone range of 13.0 mm and 11.0 mm respectively.

It is obvious from this study that the ligand is mostly more effective than the complexes against the bacteria with the exceptions of Mn(II) and Ni(II) complexes whose activities of 13.0 mm are the same as the ligand, against *E. coli* and *P. mirabilis* respectively. The lower activities of the metal complexes relative the ligand may be attributed to the degree of permeability of the cells of the bacteria or the difference in the bacteria ribosomes [26]. In addition the Cu(II) complex activity of 16.0 mm against *E. coli* is greater than that of the ligand (13.0 mm) due to chelation and π-electron delocalisation which increase the lipophilic character, favouring its permeation into the bacterial membrane, causing the death of the organism [27]. Sulfamethoxazole activities (25.0-39.0 mm) against the various bacterial isolates relative to the metal complexes (10.0-16.0 mm), show that the activities of the metal complexes are much lower with the optimum activity of about half in Cu(II) complex against *E. coli*. Thus, the ligand and Cu(II) complex exhibit broad-spectrum antibacterial activity against *Staphyloccous aureus*, *Esherichia coli* and *Proteus mirabilis* with inhibitory zones range of 12.0-13.0 and 10.0-16.0 mm respectively, proving their usefulness as potential broad-spectrum antibacterial agents.

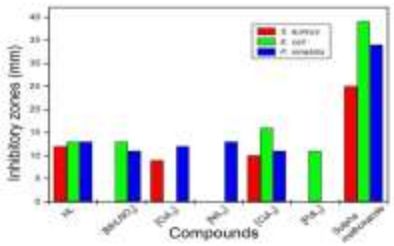

Fig 3. The comparative antibacterial activities of the complexes with the standard Antibiotic

Anticancer activity

The results of the anticancer activities are presented in Table 4, and shown in Figures 4 and 5. The metal complexes are more susceptible to the MCF-7 cells. The sensitivity of MCF-7 cells to the ligand and its Co(II), Cu(II) and Pd(II) complexes decrease as follows; CuL_2 (9.78 µM) > CoL_2 (17.48 µM) > PdF_2 (21.01 µM) > HL(26.54 µM). The Cu(II) complex activity is the best, being about $1/5^{th}$ that of Cis-platin (Figure 4). Thus, chelation enhances the cytotoxic activities of the compounds.

The colon carcinoma cells (HT-29) are not sensitive to the Pd(II) complex but are sensitive to the ligand, Co(II) and Cu(II) complexes with IC_{50} values of 46.68 µm, 43.50 µm and 17.02 µm respectively.

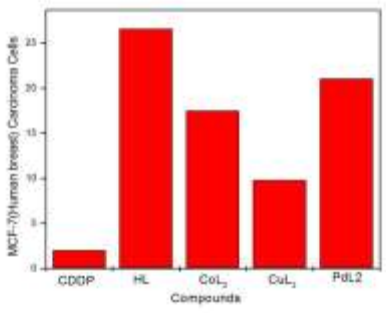

Fig 4 The inhibitory effect of the ligand, Co(II), Cu(II) and Pd(II) complexes against Human Breast Adenocarcinoma cells

The Cu(II) complex has the best activity which is about half that of Cis-platin(CDDP). The Co(II) complex activity is marginally higher than that of the ligand, being about $1/6^{th}$ that of Cis-platin and the latter's activity is about $1/7^{th}$ that of Cis-platin (Figure 5). The decreasing order of activity is; CuL_2 > CoL_2> HL.

Thus, chelation enhances cytotoxic activities. The good anticancer activity of the Cu(II) complex is attributed to its

planar geometry which avoids possible steric hindrance during physiological actions [28].

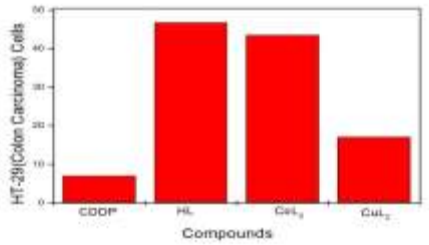

Fig 5 The inhibitory effect of the ligand, Co(II) and Cu(II) complexes against Colon Carcinoma cells

Conclusion

The ligand coordinates to the Mn(II), Co(II), Ni(II), Cu(II) and Pd(II) ions using the azomethine *N* and Chromenol *O* atoms, and the Co(II) and Ni(II) complexes are in the trans-isomeric form as shown by the IR measurements. The assignment of a 4-coordinate, tetrahedral geometry to Mn(II), Co(II), Ni(II) and Zn(II) complexes, and square-planar geometry to the Cu(II) and Pd(II) complexes is corroborated by electronic spectral measurements. The ligand and the Cu(II) complex exhibit broad-spectrum antibacterial activities *Staphyloccous aureus*, *Esherichia coli* and *Proteus mirabilis* with inhibitory zones range of 12.0-13.0 and 10.0-16.0 mm. The cytotoxic study shows that the Cu(II) complex has the best in-vitro anticancer activity against both MCF-7(human breast adenocarcinoma) and HT-29 (colon carcinoma) cells, with IC_{50} values of 9.78 µM and 17.02 µM, which are about a fifth as, and half as active as Cis-platin respectively.

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Table 1Analytical data for the compounds

Compound (Empirical formula)	Formula mass	Color	% Yield	Λ_m^*	M.pt (^oC)	Analysis (Calculated) %C	%H	%N	%M
HL ($C_{18}H_{16}NSO_2$)	309.38	Yellow	70	-	94-96	69.52 (69.80)	5.54 (5.21)	4.15 (4.53)	-
$[MnLNO_3]H_2O$ ($MnC_{18}H_{17}N_2SO_6$)	443.34	Green	60	13.0	140+	48.81 (48.77)	3.67 (3.87)	5.03 (6.32)	12.32 (12.39)
# $[CoL_2]7H_2O$ ($CoC_{36}H_{44}N_2S_2O_{11}$)	801.83	Orange	50	10.0	300+	53.94 (53.93)	4.40 (5.53)	4.05 (3.49)	7.38 (7.35)
$[NiL_2]3H_2O$ ($NiC_{36}H_{36}N_2S_2O_7$)	729.53	Brown	60	12.0	200+	59.25 (59.27)	4.69 (4.97)	4.17 (3.84)	8.12 (8.05)
$[CuL_2]3H_2O$ ($CuC_{36}H_{36}N_2S_2O_7$)	734.37	Lemon Green	60	15.0	170+	58.25 (58.88)	4.89 (4.94)	3.55 (3.82)	8.72 (8.65)
$[PdL_2]3H_2O$ ($PdC_{36}H_{36}N_2S_2O_7$)	777.20	Brown	60	18.0	176+	55.82 (55.64)	4.74 (4.67)	3.62 (3.60)	13.68 (13.69)

= hygroscopic; $*\Omega^{-1}\ cm^2\ mol^{-1}$; + = decomposition temperature

Table 2. Relevant infrared and electronic spectral data of the complexes

Compound	νOH	ν(C=N)	δC—H	ν(M—N)	ν(M—O)	Electronic transitions (kK)
HL	3417b	1650s 1618s 1581s1556s	981s	-	-	25.20, 36.80, 40.98
$[MnLNO_3]H_2O$	3500b	1644s 1617s1528s	826s	537s	414m	14.01, 25.32, 36.90, 40.0
$[CoL_2]7H_2O$	3500b	1595s 1541s	823s	534s	414m	15.30, 20.94, 25.51, 40.16.
$[NiL_2]3H_2O$	3500b	1599s 1506s	822s	542s	498s	14.71, 20.04, 25.84, 38.46.
$[CuL_2]3H_2O$	3500b	1620w1598s 1579w 1509s	825s	572s	472m	15.0, 24.07, 28.02, 33.78, 37.45
$[PdL_2]3H_2O$	3500b	1620w 1598s1561s 1501s	824m	545m	454m	15.39, 25.0, 30.12, 34.97, 40.68

Key: s = strong, m = medium, b = broad, s = strong; 1 kK = 1000 cm^{-1}

Table 3 Zones of inhibition (mm) of the compounds against various bacteria isolates

Compounds	*S.aureus*	*E. coli*	*P. mirabilis*	*K.pneumoniae*
HL	12.0±1.4	13.0±0.3	13.0±1.7	R
$[MnLNO_3]H_2O$	R	13.0±0.2	11.0±0.2	R
$[CoL_2]7H_2O$	9.0±0.0	R	12.0±1.4	R
$[NiL_2]3H_2O$	R	R	13.0±0.7	R
$[CuL_2]3H_2O$	10.0±1.4	16.0±1.4	11.0±0.5	R
$[PdL_2]3H_2O$	R	11.0±0.0	R	R
Sulfamethoxazole$^+$	25.0±2.0	39.0±0.0	34.0±2.2	R

Key: R = Resistance; + = positive standard.

Table 4. IC_{50} values of the ligand and its Co(II), Cu(II), Pd(II) complexes against MCF-7 and HT-29 cells

Compounds	MCF-7(human breast adenocarcinoma) [μM]	HT-29(colon carcinoma cells) [μM]
CDDP(Cis-platin)	2.0	7.0
HL	26.54±0.2	46.68±0.0
$[CoL_2]7H_2O$	17.48±0.0	43.50±0.1
$[CuL_2]3H_2O$	9.78 ± 0.2	17.02 ±0.0
$[PdL_2]3H_2O$	21.01±0.1	>100

Results are expressed as means (± error) of at least two independent experiments