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Biomedicinal Studies of Some Mixed Ligand Complexes of Cobalt

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ABSTRACT
The present manuscript deals the synthesis of some novel mixed ligand complexes of Copper and their characterization on the basis of melting point, elemental and spectral analysis. The newly synthesized complexes were also tested for their antibacterial, antifungal and antitumor activity in-vitro and their results of screening clearly indicating them as potent biomedicinal agents.
Key words: *Mixed ligand Complexes, antibacterial, antifungal, antitumor activity.*

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INTRODUCTION

The importance of metal based drugs lies in the fact that they are essential components for various physico-chemical processes occurring in living system [1-6].Coordination chemistry forms the backbone for the major part of the current researches in chemistry. Coordinated metal ions incorporated in the structure of enzymes are responsible for their action [7-10]. The transition metal ions are known to persist in biological systems by coordination with numerous enzymes containing the heme and related structures such as catalases, peroxidases and cytochromes. The iron containing proteins, ferritin, transferrin and hemosiderin are known to predominate in biological systems. Mixed ligand complexes reported as lymphocyte activators are known for their- importance [11-15].

In recent years, there has been increased interest in the study of mixed-ligand complexes [16-18]. Such species are made up of the central metal ion and two or more different suitable ligand molecule, other than solvent.These mixed-ligand complexes are of considerable interest in biological chemistry, because mixed-chelation occurs commonly in biological fluids, as millions of potential ligands are likely to compete for metal ions found in vivo, i.e., Na, K, Mg, Ca, Fe, Co, Cu, Zn and Mo. The mixed-ligand complexes are intermediates in ligand displacement reactions as well as in ligand catalyzed complex formation reactions. Such complexes also create specific structures and have been implicated in the storage and transport of active substances through membranes and the phenomena are strongly dependent on the formation of such species and the nature of involved metal ions [19-21].

The present manuscript contains the details of the synthesis of some mixed ligand complexes of Co and their biomedicinal studies.

MATERIAL AND METHOD

The primary ligands i.e. 2, 2'-bipyridyl and 1,10- phenanthroline will be taken as such (AR grade) and will be used while preparing the mixed ligand complexes Co(II) salts while secondary Ligands (Amides) will be synthesized by taking 1:1 molar ratio of thioglycolic acid and 2-aminopyridine, 2-aminoadinine, 2-aminoguanine and 2-aminocytosine by refluxing the components for appropriate periods and the resultant product will be crystallized. The binary complexes of Co(II) with corresponding thioamides of 2-aminopyridine, 2-aminoadinine, 2-aminoguanine, and 2-aminocytosine will be synthesized by taking 1:2 molar ratio of metal ion and the amide and refluxing the components for suitable period and crystallized.

Co(II)bipridylthioamide and Co(II)phenanthrolinethioamide

Cobalt chloride hexahydrate (0.005 ml mole) was dissolved in 30 ml of double distilled water in a round bottomed flask. The pH of the metal salt solution was adjusted between 5.0 and 5.5. 10 ml of 10% hydroxylamine hydrochloride were also added to check the possible oxidation of Co(II) to Co(III). 30 ml of ethanolic solution of ligand (bipridylor phenanthroline, 0.005 moles) was added to the metal salt solution. The contents were warmed and to this 30 ml of thioamide (0.005 mole) solution in ethanol was

added. In both cases a deep reddish brown complex was immediately obtained. The complex was digested on a boiling water bath for about 30 minutes. It was filtered under suction, washed with hot water, 3-4 times with ethanol and finally with ether. The complex was dried in an oven at 110°C.

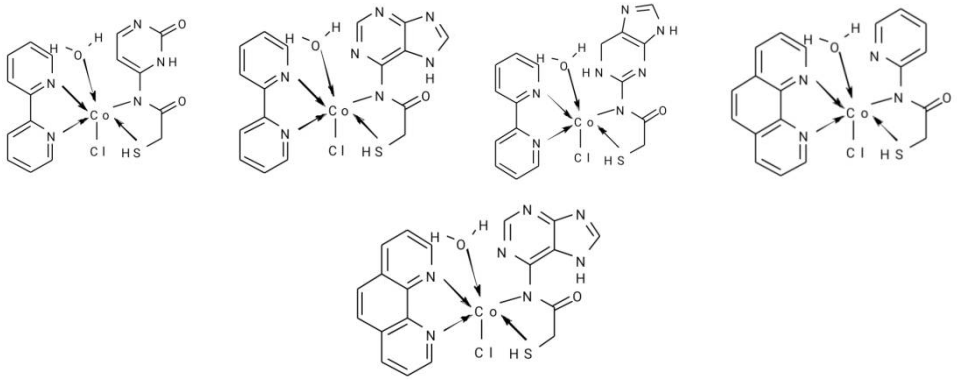

Fig.-1: Structure of Mixed Ligand Complexes of Cobalt

Antibacterial Activity

Antibacterial activity of these compounds was determined by disc-diffusion method (22). In this technique, the filter paper (Whatmann No. 1) sterile discs of 5 mm diameter, impregnated with the test compounds (10μg/ml of ethanol) were placed on the nutrient agar plate at 37°C for 24 hours. The inhibition zones around the dried impregnated discs were measured after 24 hrs. The activity was classified as "highly active" (diameter= >14mm); "moderately active" (diameter = 10-14 mm) and "slightly active" (diameter 6-10 mm). The diameter less than 6 mm was regarded as inactive.

Antifungal Activity

The antifungal activity of these compounds was determined by agar plate method; (23) using four concentrations *viz*; 10, 20, 50 and 100 μg/ml of test compounds against human pathogenic fungal strains, *Aspergillusflavus* and *Aspergillusnigar*. One 1 ml of each compound was poured into a petri-dish having about 20-25 ml of molten potato-dextose agar medium. As the medium gets solidify, petridishes were inoculated separately with the fungal isolates and kept at 27° for 96 hrs. All the values (% inhibition) were recorded. The percentage inhibition of various organoantimony compounds were calculated by using following mathematical equations (24).

$$\text{Percentage (\%) Inhibition} = \frac{C - T}{C} \times 100$$

Here, C = Diameter of fungus in control; T = Diameter of fungus in test compounds

Antitumor Activity

The human Breast Cancer cell line (MCF-7) was co-incubated with the test compounds at 1 μg/ml doses for 96 hrs and the cell growth count was measured by MTT assay as described below (25). 17β estradiolused as positive control and culture medium as negative control was used. The cell proliferation activity assay was carried out to estimate the effect of test compounds on the growth of tumor cells *in-vitro*. Measurement of cell viability and proliferation forms the basis for this *in-vitro* assay. The reduction of tetrazolium salt is now widely accepted as reliable way to examine cell proliferation. The yellow coloured tetrazolium, MTT [3-(4,5-dimethyl thiazol-2yl)-2,5-diphenyltetrazolium-bromide] reduced by metabolically active cells partially by the action of dehydrogenase enzymes to generate reducing equivalent such as NADH and NADPH. The resulting intracellular purple colour zones was solubilized and quantified by spectrophotometer method. When metabolic events lead to necrosis or apoptosis in cell, the MTT method measures the cell viability. The assay gives low background absorbance values in the absence or necrosis of the cells. The MTT [3-(4,5-dimethylthiazol-2yl)-2,5-diphenyltetrazolium bromide] was dissolved in PBS at a concentration of 5mg/ml. The 50 μl of the MTT solution was added to each well of the 96 well culture plate containing the 100 μl culture medium and incubated at 37°C for 4 hrs. The medium was then removed carefully without disturbing the purple coloured zone of crystals. Then 50 μl of Dimethyl Sulphoxide (DMSO) was added to each well and mixed thoroughly to dissolve the crystals of the purple coloured zone. The plates were then read on a microplate reader at a wave length of 670 nm. The readings were presented as ODC optical density). The growth inhibition of the cells by the compounds was listed in tables. Here the cell proliferative activity on MCF-7 cell line by using positive and negative control was quantified.

RESULTS AND DISCUSSION

The mixed-ligand complexes of Co(II) ions are appreciably soluble in ethanol and slightly soluble in nitrobenzene, acetone etc. These complexes dissolve readily in acetic acid. All these complexes do not melt sharply but decomposes above 150°C. Their conductance measurements in glacial acetic acid indicate that these mixed ligand complexes are non-electrolyte. Molecular weight determinations of these complexes correspond to their monomeric nature in solution. The mixed-ligand complexes of Co(II) ion are insoluble in common organic solvents and do not, melt up to 250°C. This may be indicative of their polymeric nature. The complexes show proper ratios of elements as in their data of elemental analysis.

Spectral Analysis

The spectral analysis of complexes covers its IR, and NMR analysis as per standard norms. The Infrared absorption spectra of bipridyl, phenanthroline, thioamide and all mixed-ligand complexes under investigation have been obtained in KBr pallet using Perkin-Elmer model-577 IR absorption spectrophotometer.

IR spectra of 2.2'-bipridyl, 1, 10-phenanthroline

These ligands and their metal complexes have been extensively studied through infrared absorption spectroscopy. By looking to the structure one would expect characteristic vibrations due to heterocyclic rings in Bipy, and due to aromatic heterocyclic rings in phenanthroline. The characteristic vibrations are given in Tables. Heterocyclic aromatic compounds such as pyridine have been reported to show somewhat similar set of bands. -C-H stretching vibrations, in pyridine has been reported to occur at near 3070-3020 cm^{-1}. 2,2'-Bipyridyl shows absorption band near 3060 cm^{-1} due to characteristic CH stretching vibration. Aromatic C=C stretching vibrations have been reported to occur in the region 1650-1450 cm^{-1}, actual position of these band;-, show wide violations. In aromatic compounds band at 1580 cm^{-1} is reported to be very weak and difficult to detect but its intensity is enhanced by external conjugation. Bipy shows a band of medium intensity at 1582 cm^{-1} probably it has derived its intensity from interaction of p-electrons of the nitrogen atom of the ring. In other words 1582 cm^{-1} absorption band carries some contribution due to ring C=N vibrations also. 1,10- Phenanthroline shows absorption band at 1590 cm^{-1}. This may also carry contribution due to ring C=N vibrations. Another characteristic C=C, stretching vibration has been reported to occur near 1450 cm^{-1}. Bipy and Phenanthroline show absorption band at 1455 and 1450 cm^{-1} respectively due to C=C stretching vibrations. An absorption band in the region 1525-1475 cm^{-1} usually close to 1500 cm^{-1} has been reported to be due to C=C stretching vibration. Phenanthroline shows absorption band at 1495 cm^{-1}.

^{1}H and ^{13}C NMR Spectra:

^{1}H NMR spectra of the mixed ligand complexes was recorded in $CDCl_3$ using TMS as an internal reference at 25°C. The details of signals of only one series of mixed ligand complexes have been explained here which clearly indicates the presence of aromatic hydrogens, amide hydrogen as per signals. The details are as under.

Complex-1:^{1}H-NMR in ppm (400MHz; Solvent: $CDCl_3$): δ 8.59-7.12 (12H, m, 2-pyridine CH) 3.33 (2H, s, methylene) **^{13}C-NMR** in ppm (100 MHz; Solvent: $CDCl_3$): δ 166.1, 149.8, 144.4 123.6, 135.7,123.6, 117.5, 110.8, 77.8, 59.8, 41.9, 35.0.

Complex-2:^{1}H-NMR in ppm (400MHz; Solvent: $CDCl_3$): δ 8.55-7.14 (12H, m, 2-pyridine CH), 7.50 (2H, s, CH, aldimine) 3.4 (2H, s, methylene) **^{13}C-NMR** in ppm (100 MHz; Solvent: $CDCl_3$): δ 166.1, 149.8, 144.4 125.6, 137.7,126.6, 118.5, 79.8, 57.8, 42.9.

Complex-3:^{1}H-NMR in ppm (400MHz; Solvent: $CDCl_3$): δ 8.59-7.12 (12H, m, 2-pyridine CH), 7.50 (2H, s, CH, aldimine), 3.33 (2H, s, methylene) 1.5 (1H, s, methine)**^{13}C-NMR** in ppm (100 MHz; Solvent: $CDCl_3$): δ 166.1, 149.8, 144.4 123.6, 135.7,123.6, 117.5, 110.8,71.1, 64.4, 48.2.

Complex-4: ^{1}H-NMR in ppm (400MHz; Solvent: $CDCl_3$): δ 8.0 (1H, s, NH sec. amide) 7.50 (2H, CH, aldimine) 8.59-7.12 (12H, m, 2-pyridine CH) 3.33 (2H, s, methylene) **^{13}C-NMR** in ppm (100 MHz; Solvent: $CDCl_3$): δ 166.1,, 165.5163.1, 149.8, 144.4 123.6, 135.7,123.6, 117.5, 110.8, 77.8, 59.8, 41.9, 35.0.

Complex-5:^{1}H-NMR in ppm (400MHz; Solvent: $CDCl_3$): δ 8.57-7.22 (12H, m, 2-pyridine CH) 3.35 (2H, s, methylene) **^{13}C-NMR** in ppm (100 MHz; Solvent: $CDCl_3$): δ 168.1, 148.8, 143.4 125.6, 133.7, 3520.

Complex-6: ^{1}H-NMR in ppm (400MHz; Solvent: $CDCl_3$): δ 8.51-7.18 (9H, m, aromatic CH), 7.52(2H, s, CH, aldimine) 3.4 (2H, s, methylene) **^{13}C-NMR** in ppm (100 MHz; Solvent: $CDCl_3$): δ 168.1, 149.8, 144.4 125.6, 137.7,126.6, 118.5, 72.8, 57.8, 44.9.

Complex-7: ^{1}H-NMR in ppm (400MHz; Solvent: $CDCl_3$): δ 8.59-7.12 (9H, m, phenanthroline, CH), 7.49(2H, s, CH, aldimine), 3.35 (2H, s, methylene) 1.7 (1H, s, methine)**^{13}C-NMR** in ppm (100 MHz; Solvent: $CDCl_3$): δ 168.1, 149.8, 144.4 123.6, 135.7,123.6, 117.5, 110.8,71.1, 64.4, 48.2.

Complex-8: ^{1}H-NMR in ppm (400MHz; Solvent: $CDCl_3$): δ 8.2 (1H, s, NH sec. amide)8.59-7.12 (9H, m, aromatic CH), 7.50 (2H, CH, aldimine) 3.33 (2H, s, methylene) **^{13}C-NMR** in ppm (100 MHz; Solvent: $CDCl_3$): δ 168.1,, 165.5163.1, 149.8, 144.4 123.6, 135.7,123.6, 117.5, 110.8, 77.8, 59.8, 41.9, 35.0.

Anti-bacterial activity of Mixed Ligand Complexes of Cobalt

Antibacterial activity of these compounds was tested against three human pathogenic bacteria *viz*. *Pseudomonas aeruginosa, Staphylococcus aureus* and *Klebsiela pneumonia*. The Complex No. **3,5,6** and **8** shows highest antibacterial activity against *Kleibsiela pneumonia* while the other compound shows moderate activity against this bacterium. In case of *Staphylococcus aureus*the compounds **2**, **3** and **7** shows highest activity while the other compounds shows moderate activity. The activity in case of *Pseudomonas aeruginosa*is highest by the compound **1, 4** and 5 and rest of the compounds shows moderate to low activity. The difference in antibacterial activity of all these compounds is generally due to variation in ligands with thio group. The other factor of higher activity is the oxidation state of Metal. The results of antibacterial activity of these compounds are listed in Table-2.

Anti-fungal activity of mixed ligand complexes of Cobalt

The antifungal activity of newly synthesized mixed ligand complexes of Zn were tested against the known fungus culture of *Aspergillusflavus*and *Aspergillusnigar*and the percentage inhibition calculated by the colony diameter of control and test sample. The antifungal activity was carried out using four concentrations. *viz*. 10, 20, 50 and 100 μg/ml of the test compounds. At 10μg/ml conc. of the compounds, compounds **1, 2** and **4** shows highest activity in case of Aspergillusflavus while complex 6, and 7 shows highest activity. The rest complexes exhibit moderate to low activity in case of both fungal strains. At 20 μg/ml conc. of test compounds, compounds **1, 2** and **4** shows highest activity in Aspergillusflavus and complex 4, 6 and 7 show best activities while the rest of the compounds show moderate antifungal activity. At 50μg/ml concentrations, approximately all complexes show highest activity than the other compounds. At 100 μg/ml conc., the compounds show highest antifungal activity in both the fungal strains. The variation in percentage inhibition of these compounds against fungal stains is due to variation in ligands group attached. The Results are summarized in Table-3 (A-D).

***In-vitro* antitumor activity of mixed ligand Complexes of Cobalt**

The mixed ligand complexes of Co were tested for their *in-vitro* antitumor activity against human breast adenocarcinoma cell line (MCF-7). The results of bioassay show that few of these compounds (complex **1, 2,** and **6)** exhibit *in-vitro* antitumor activity. The efficacy of different compounds varies with the type of ligands and presence of nitrogen and sulphur content. The inhibition percentage (%) was compared by positive and negative control and the activity has been reported in the form of cell count.The compound generally interacts with the receptor site of multienzyme complex responsible for the cytostatic and cytotoxic conditions. The compound can easily bind with the receptor site. It may be noted that the compound generally binds with nitrogen 7 position of purine bases in DNA molecule and form complexes with DNA strands affecting replication and transcription of DNA molecule and stop the cell division along with protein synthesis.

Table-1 Physico-chemical analysis of Mixed ligand Complexes of Cobalt

S.N.	Complexes formula	Molecular Weight	Exact Weight	Melting/ Decomposition Point(ºC)	Elemental Analysis			
					% C	% H	% N	% S
1	$C_{17}H_{17}ClN_4O_2SCo$	435.79	435.00	152	46.85	3.87	12.67	7.25
2	$C_{17}H_{16}ClN_7O_2SCo$	476.80	476.01	174	42.82	3.34	20.29	6.63
3	$C_{17}H_{18}ClN_7O_2SCo$	478.82	478.02	170	42.64	3.74	20.20	6.61
4	$C_{16}H_{16}ClN_5O_3SCo$	452.78	451.99	166	42.44	3.51	15.25	6.98
5	$C_{19}H_{17}ClN_4O_2SCo$	459.81	459.00	162	49.63	3.67	12.02	6.88
6	$C_{19}H_{16}ClN_7O_2SCo$	500.82	500.01	178	45.57	3.18	19.33	6.32
7	$C_{19}H_{18}ClN_7O_2SCo$	502.84	502.02	180	45.38	3.56	19.25	6.30
8	$C_{18}H_{16}ClN_5O_3SCo$	476.80	475.99	176	45.34	3.34	14.49	6.63

Table-2: Antibacterial Activity of Mixed Ligand complexes of Cobalt

S. N.	Compounds	Control	*Pseudomonas aeruginosa*	*Staphylococcus aurius*	*Klebsiela pneumonia*
1.	$C_{17}H_{17}ClN_4O_2SCo$	–	+++	++	++
2.	$C_{17}H_{16}ClN_7O_2SCo$	–	++	+++	++
3.	$C_{17}H_{18}ClN_7O_2SCo$	–	++	+++	+++
4.	$C_{16}H_{16}ClN_5O_3SCo$	–	+++	++	++
5.	$C_{19}H_{17}ClN_4O_2SCo$	–	+++	++	+++
6.	$C_{19}H_{16}ClN_7O_2SCo$	–	++	++	+++
7.	$C_{19}H_{18}ClN_7O_2SCo$	–	++	+++	++
8.	$C_{18}H_{16}ClN_5O_3SCo$	–	++	+	+++
	+ = 6-10 mm; +++ = 14 mm ; ++ = 10-14 mm; – = Inactive (Control) Ampicillin				

Table-3: Anti-Fungal Activity of Mixed Ligand complexes of Cobalt

(A)	Activity at 10 μg/ml of conc. of test compounds				
S. N.	Compounds	*Aspergillus nigar*		*Aspergillus flavus*	
		Colony Dia. (mm)	% Inhibition A. nigar	Colony dia (mm)	% Inhibition A. flavus
1.	$C_{17}H_{17}ClN_4O_2SCo$	0.8	73.3	1.0	50.0
2.	$C_{17}H_{16}ClN_7O_2SCo$	0.7	76.7	1.4	30.0
3.	$C_{17}H_{18}ClN_7O_2SCo$	1.2	60.0	1.0	50.0
4.	$C_{16}H_{16}ClN_5O_3SCo$	0.5	83.3	1.5	25.0
5.	$C_{19}H_{17}ClN_4O_2SCo$	1.2	60.0	1.0	50.0
6.	$C_{19}H_{16}ClN_7O_2SCo$	1.4	53.3	0.8	60.0
7.	$C_{19}H_{18}ClN_7O_2SCo$	1.2	60.0	0.8	60.0
8.	$C_{18}H_{16}ClN_5O_3SCo$	1.2	60.0	1.0	50.0
9.	Control	3.0	–	2.0	–
(B)	Activity at 20 μg/ml of conc. of test compounds				
S. N.	Compounds	*Aspergillusnigar*		*Aspergillusflavus*	
		Colony dia (mm)	% Inhibition A. nigar	Colony dia (mm)	% Inhibition A. flavus
1.	$C_{17}H_{17}ClN_4O_2SCo$	0.5	83.3	0.7	65.0
2.	$C_{17}H_{16}ClN_7O_2SCo$	0.5	83.3	1.2	40.0
3.	$C_{17}H_{18}ClN_7O_2SCo$	1.0	66.6	0.8	60.0
4.	$C_{16}H_{16}ClN_5O_3SCo$	0.4	86.7	0.6	70.0
5.	$C_{19}H_{17}ClN_4O_2SCo$	0.7	76.7	1.0	50.0
6.	$C_{19}H_{16}ClN_7O_2SCo$	0.6	80.0	0.6	70.0
7.	$C_{19}H_{18}ClN_7O_2SCo$	0.7	76.7	0.4	80.0
8.	$C_{18}H_{16}ClN_5O_3SCo$	0.6	80.0	0.8	60.0
9.	Control	3.0	–	2.0	–
(C)	Activity at 50 μg/ml of conc. of test compounds				
S. N.	Compounds	*Aspergillusnigar*		*Aspergillusflavus*	
		Colony dia (mm)	% Inhibition A. nigar	Colony dia (mm)	% Inhibition A. flavus
1.	$C_{17}H_{17}ClN_4O_2SCo$	0.4	86.6	0.6	70.0
2.	$C_{17}H_{16}ClN_7O_2SCo$	0.2	93.3	0.8	60.0
3.	$C_{17}H_{18}ClN_7O_2SCo$	0.7	76.7	0.5	75.0
4.	$C_{16}H_{16}ClN_5O_3SCo$	0.4	86.6	0.5	75.0
5.	$C_{19}H_{17}ClN_4O_2SCo$	0.5	83.3	0.8	60.0
6.	$C_{19}H_{16}ClN_7O_2SCo$	0.4	83.7	0.2	90.0
7.	$C_{19}H_{18}ClN_7O_2SCo$	0.5	83.3	0.2	90.0
8.	$C_{18}H_{16}ClN_5O_3SCo$	0.5	83.3	0.8	60.0
9.	Control	3.0	–	2.0	–

(D)	Activity at 100 μg/ml of conc. of test compounds				
S. N.	Compounds	*Aspergillus nigar*		*Aspergillus flavus*	
		Colony dia (mm)	% Inhibition A. nigar	Colony dia (mm)	% Inhibition A. flavus
1.	$C_{17}H_{17}ClN_4O_2SCo$	0.2	93.3	0.4	80.0
2.	$C_{17}H_{16}ClN_7O_2SCo$	0.1	97.7	0.5	75.0
3.	$C_{17}H_{18}ClN_7O_2SCo$	0.4	86.6	0.2	90.0
4.	$C_{16}H_{16}ClN_5O_3SCo$	0.1	96.7	0.3	85.0
5.	$C_{19}H_{17}ClN_4O_2SCo$	0.2	93.3	0.4	80.0
6.	$C_{19}H_{16}ClN_7O_2SCo$	0.1	96.6	0.1	95.0
7.	$C_{19}H_{18}ClN_7O_2SCo$	0.1	96.7	0.1	95.0
8.	$C_{18}H_{16}ClN_5O_3SCo$	0.4	86.6	0.3	85.0
9.	Control	3.0	–	2.0	–

Table-4: *In-vitro* antitumor activity of Mixed Ligand complexes of Cobalt

S. N.	Compounds	Cell No. x 10^4	Activity
1.	$C_{17}H_{17}ClN_4O_2SCo$	9.29±0.89	+
2.	$C_{17}H_{16}ClN_7O_2SCo$	9.45±0.67	+
3.	$C_{17}H_{18}ClN_7O_2SCo$	12.97±1.22	–
4.	$C_{16}H_{16}ClN_5O_3SCo$	12.34±1.04	–
5.	$C_{19}H_{17}ClN_4O_2SCo$	11.89±1.16	–
6.	$C_{19}H_{16}ClN_7O_2SCo$	9.89±0.51	+
7.	$C_{19}H_{18}ClN_7O_2SCo$	13.91±1.27	–
8.	$C_{18}H_{16}ClN_5O_3SCo$	12.34±1.04	–
9.	Negative control	10.21±1.01	–
10.	Positive control	40.26±3.23	–

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Conflict of Interest
There is no conflict of interest between authors regarding academic, commercial, financial, personal and professionally relevant to the work.

Author's Contribution
Synthesis, preliminary characterization and antitumor studies were performed by the Om Kumari and Arvind Kumar while biomedicinal studies were performed by Dinesh Kumar Sharma and Ravi Kant.

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Ethics Statement
Not Applicable as the study performed in-vitro and in-silico.

Informed Consent
Not Applicable

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